SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Velcade®
Name of Active Ingredient(s)	JNJ-26866138 Bortezomib

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Protocol No.: 26866138MMY3012 and 26866138MMY3013

Title: Bortezomib as Consolidation Therapy in Patients with Multiple Myeloma

- Study 26866138MMY3012: Bortezomib in the consolidation therapy with patients at an age of ≤60 years with multiple myeloma ("Bortezomib in der Konsolidierungstherapie bei Patienten im Alter von ≤60 Jahren mit Multiplem Myelom")
- Study 26866138MMY3013: Bortezomib in the consolidation therapy with patients at an age of 61–75 years with multiple myeloma ("Bortezomib in der Konsolidierungstherapie bei Patienten im Alter von 61-75 Jahren mit Multiplem Myelom")

EudraCT Number: 2005-004948-31 and 2005-004947-73

NCT No.: NCT00416273 and NCT00416208

Clinical Registry No.: CR006124 and CR006127

Principal Investigators:

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Study Centers: A total of 47 study centers in Germany were considered for evaluation of which 36 sites can be attributed to both studies. Overall, 43 sites belong to MMY3012 and 40 sites to MMY3013.

Publication (Reference): none

Study Period: 13 October 2006 to 24 May 2013; database lock: 30 June 2014

Phase of Development: 3

Objectives: In Western Europe, symptomatic patients suffering from multiple myeloma (MM) and suitable for high-dose therapy are currently offered high-dose chemotherapy (HD-CT) and subsequent autologous stem cell transplantation (SCT). However, therapeutic success in this strategy is still limited by high relapse rates due to residual tumor.

Bortezomib (Velcade®) is currently approved for the treatment of multiple myeloma in the USA. In the EU it is approved as monotherapy and for combination therapy with pegylated liposomal doxorubicin or dexamethasone in patients with progressive MM who have received at least one prior therapy and who have undergone or are not eligible for autologous stem cell transplantation (ASCT), in combination with melphalan and prednisone in patients with previously untreated MM who are not eligible for ASCT, and in combination with dexamethasone or dexamethasone and thalidomide in patients with previously untreated MM eligible for ASCT. Moreover, it has been explored in the treatment of therapy-requiring,

ASCT-eligible but treatment-naïve patients in study 26866138MMY2031 in combination with dexamethasone and cyclophosphamide. The present analysis addresses its use in MM consolidation therapy following HD-CT and SCT in patients aged ≤60 years (study 26866138MMY3012) and in patients aged 61 to 75 years (study 26866138MMY3013).

- Primary objective was assessment of progression-free survival (PFS) defined in the protocol as 'determination of event-free survival with and without bortezomib consolidation therapy from the day of the first chemotherapeutic, myeloma-specific therapy measure up to the occurrence of progression/ relapse or up to the occurrence of death'.
- Important secondary objectives were assessment of time to next treatment defined as event-free survival (EFS, i.e., survival from first day of administration of the first myeloma-specific chemotherapy to start of a new chemotherapy, or to death), response rates, overall survival (OS), time to progression (TTP), occurrence of toxicities during consolidation therapy, quality of life (QoL) in patients receiving or not receiving consolidation therapy, proportion of patients experiencing skeletal-related events (SREs) and time to occurrence of an SRE. Additional secondary objectives were evaluation of the prognostic significance of specific cytogenetic parameters and analysis of response rates in the treatment arms in patients with specific cytogenetic changes.

Methodology: Both studies followed a randomized two-arm, open-label, prospective, multi-center phase 3 design comparing bortezomib consolidation therapy (bortezomib treatment arm) and observation (observational arm). Randomized patients of the bortezomib arms received consolidation therapy for 20 weeks, followed by a Concluding Visit (end of treatment, EoT) scheduled for Week 25 and by a post-observation follow-up period of 30 to 60 months. Patients of the observational arms were observed analogously. Three interim analyses have been performed. Administration of anti-neoplastic agents including hormones and immunomodulators (e.g., interferon, interleukin) used for MM treatment as well as systemic corticosteroids in a dose of >10 mg/d prednisolone equivalent was prohibited during the bortezomib treatment/observation period. Adjunctive local radiotherapy and administration of bisphosphonates according to DSMM recommendations was allowed.

Number of Patients (planned and analyzed): Combining studies 26866138MMY3012 and 26866138MMY3013, recruitment of 385 patients was planned. This sample size was nearly reached: Overall, 380 patients were consented and 371 patients were randomized (9 screening failures) with 186 patients (50.1%) to the bortezomib arms (109 in study 3012 and 77 in study 3013) and 185 patients (49.9%) to the observational arms (108 in study 3012 and 77 in study 3013). Nine randomized Patients dropped out after randomization but prior to Day 1, i.e., prior to start of treatment/observation. Further 77/371 (20.8%) randomized patients terminated the treatment/observational period prematurely. Follow-up data are available for 321/371 randomized patients (86.5%).

Data Sets Analyzed			
	Bortezomib Arm (N=186); n (%)	Observational Arm (N=185); n (%)	Total (N=371); n (%)
Planned			385
Screened			380
Randomized	186 (100)	185 (100)	371 (100)
Safety population	186 (100)	185 (100)	371 (100)
Efficacy population	177 (95.2)	180 (97.3)	357 (96.2)
Safety population follow-up	150 (80.6)	171 (92.4)	321 (86.5)
Efficacy population follow-up	150 (80.6)	171 (92.4)	321 (86.5)
NOTE: Intent-to-treat population includes all randomized patients NOTE: Safety population includes all randomized patients who received at least 1 dose of study agent			

Diagnosis and Main Criteria for Inclusion: Men and women suffering from MM ≥18 to 75 years of age and pre-treated with a front-line therapy of SCT induction and melphalan HD-CT with subsequent SCT. Eligible patients had to be free of disease progression after HD-CT and free of other severe concomitant diseases. Written consent to study participation as documented by signing the informed consent form (ICF) prior to enrollment was mandatory.

Test Product, Dose and Mode of Administration, Batch No.: Patients in the bortezomib arms received 4×4 intravenous (IV) bolus injections of 1.6 mg/m^2 bortezomib (Velcade®). For each of 4 treatment cycles and when the patient's weight changed for more than 10% the bortezomib dosage had to be recalculated. Bortezomib solution was freshly prepared for each injection according to instructions.

Batch numbers:

- **MMY3012:** 7LZSB00 (Reference No. 361133), 7HZT100 (Reference No. 360607), 7DZT802 (Order No. 354621), 6CBS100 (Order Nos. 354484 and 352589), 6CBS501 (Order No. 351076), V06PE9673 (Shipping Order No. P06-02065, Lot No. 5FBS501), V06PB9515 (Shipping Order No. P06-01873; Lot No. 4IBSJ00)
- **MMY3013:** 360609 (identical with reference no., Lot No. 8DZSX00), 6CBS100 (Order No. 352861), 6CBS501 (Order No. 351077), V06PE9679 (Shipping Order No. P06-02073; Lot No. 5FBS501)

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable (Observation only)

Duration of Treatment: Bortezomib was administered in 4 treatment cycles comprising 20 weeks in total. During each cycle patients received 4 IV bolus injections of 1.6 mg/m^2 bortezomib administered in weekly intervals followed by a 13 days resting period. An end of treatment (EoT) Concluding Visit was done during Week 25.

Criteria for Evaluation: Demographic parameters collected at baseline comprised gender, age, body height and weight, body surface area (BSA), body mass index (BMI) and Karnofsky index. Furthermore, medical history was recorded with a special focus on medical history of MM (primary diagnosis, result of cytogenetic analysis, previous treatment, stem cell mobilization, HD-CT and SCT and response to previous treatments). Response to treatment had to be assessed according to EBMT (European Society for Blood and Marrow Transplantation) criteria with an additional criterion of 'very good partial response' (VGPR). Assessment of disease progression during the study was based on laboratory determination of M protein in serum and urine and immunofixation. Cases of complete response (CR) during the treatment/observation period had to be verified by bone marrow analysis at the EoT Concluding Visit (Week 25). QoL was assessed by means of validated questionnaires (EORTC QLQ-C30 and EORTC EQ-5D). Toxicities and other (serious) adverse events (AEs, SAEs) were documented in the case report form (CRF) throughout the entire study period. Occurrence of SREs defined as pathological fracture, spinal cord compression, radiotherapy of or surgery due to a bone lesion was recorded in the CRF at the EoT Concluding Visit and during the post-observation follow-up period. Additional safety parameters (physical examination, vital signs, Karnofsky index, safety laboratory, electrocardiograms [ECGs], concomitant medication) had to be documented in the CRF throughout the study.

Statistical Methods: Sample size was calculated based on the primary endpoint on the assumption of a median PFS of 21 months in the observational arms vs 30 months in the bortezomib arm. For a level of significance of α=5% and a power of 80%, the final analysis was to be performed on 252 patients. Considering expected survival times and a drop-out rate of 7%, enrollment of 385 patients was planned.
The study was planned to confirm superiority of bortezomib treatment over observation. To this end, a group-sequential (multistage) survival time approach including three interim assessments was chosen based on an O'Brien & Fleming α-spending function. The primary endpoint (PFS) has been tested using the Cox proportional hazards regression model log-rank test controlling for age (≤60 vs >60 years), presence of cytogenetic changes and best response to previous treatment for the intent-to-treat (ITT) patient population. The ITT efficacy analysis set (ES) comprises all patients enrolled who have not withdrawn consent to study participation. Survival data have been analyzed using Cox proportional hazards model to account for the effect of explanatory variables (e.g., age, presence of cytogenetic changes and best response to previous therapy) on PFS. Furthermore, survival times have been calculated using Kaplan-Meier nonparametric estimates of the survival distribution function. Secondary endpoints EFS, OS and TTP have been analyzed similarly. QoL has been analyzed according to EORTC guidelines comparing results for both groups per visit. Additional explorative subgroup analyses have been performed to evaluate prognostic parameters influencing efficacy.

Efficacy parameters have also been analyzed for the per-protocol analysis set (PPS), excluding patients with major protocol violations. Safety analyses were performed on the safety analysis set (SS) comprising all patients enrolled. Separate efficacy and safety analysis sets have been evaluated for all patients in the treatment/observation period and for patients entering the follow-up period.

Statistical programming and analyses were performed using the statistical software system SAS®. Three interim analyses have been performed: the first after 200 patients had completed the treatment/ observation period (i.e., Week 25), the second after all randomized patients had completed the treatment/observation period (i.e., Week 25) and the third 12 months after the last patient had completed the treatment/observation period. Results of each interim analysis have been reported in separate statistical reports.

One of the changes to planned analyses was analysis of OS also as part of the second and the third interim analysis. Other changes comprise clarification of the PPS definition in the final SAP (exclusion of patients with clinically relevant protocol violations, only). For PFS, EFS, OS and TTP additional analyses from time of randomization were performed as part of final analyses. Analysis of secondary endpoint duration of response (DOR) defined as time between day of first assessment of at least Minimal Response (MR) after start of therapy and day of documentation of a therapy-requiring MM progression/relapse was not performed because MR start date according to this definition was prior to study inclusion and had not been documented in the CRF. Toxicities were recorded and evaluated as treatment-emergent (serious) adverse events TE(S)AEs. Prognostic factors considered in subgroup analyses and for Cox regression analyses were redefined in the final SAP. Subgroup analyses described in the protocol but not performed comprise evaluation of level of β2-microglobulin, CRP and LDH, performance of prior radiotherapy and gender. Instead, additional subgroup and Cox regression analyses with new definitions of best response and cytogenetic changes have been performed performed in order to accommodate current knowledge on prognostic factors. Patients medical history for baseline comparison of study arms were implemented, comprising evaluation of number of cycles of first-line induction therapy in bortezomib-pre-treated versus –naïve patients, best response prior to study inclusion in bortezomib-pre-treated versus –naïve patients and best response in patients with single vs. double ASCT. Furthermore, analysis of post-progression survival was implemented for final analysis.

RESULTS:

STUDY POPULATION:

- Nine randomized patients dropped out already during the screening phase, i.e., after randomization but prior to Day 1 and thus did not enter the treatment/observation period nor did they receive study agent.
- Premature termination during the treatment/observation period was reported in 77/371 randomized patients (20.8%): 50/186 (26.9%) of the bortezomib arms vs. 27/185 (14.6%) of the observational arm.
- During follow-up 19/371 patients dropped out (9/186 [4.8%] bortezomib vs. 10/185 [5.4%] observation) due to withdrawal of consent.

Reasons for withdrawal during the treatment/observation period were progression of MM in 24/371 (6.5%) patients (2.7% bortezomib vs. 10.3% observation), occurrence of an AE in 19/371 (5.1%; 9.7% bortezomib vs. 0.5% observation) or an SAE in 7/371 (1.9%: all bortezomib) and protocol violations in 16/371 (4.3%: 7.0% bortezomib vs. 1.6% observation). One patient of the observational arms was lost to follow-up and 11/371 (3.0%) withdrew their consent to study participation (4.8% bortezomib vs. 1.1% observation). “Other” reasons were documented for 11/371 (3.0%) patients (4.3% bortezomib vs. 1.6% observation). In summary, the drop-out rate was higher in the bortezomib arms than in the observational arm). In the observational arm, most patients dropped out due to MM progression. In the bortezomib arm, most patients dropped out due to occurrence of an AE or were withdrawn because of protocol violations.

- 285/371 randomized patients (76.8%) completed the treatment/observation period (132/186 [71.0%] bortezomib vs. 153/185 [82.7%] observation).
- 302/371 patients (81.4%) completed the follow-up period (141/186 [75.8%] bortezomib vs. 161/185 [87.0%] observation).

A total of 37/371 patients (10%) were found to have major protocol violations, most of whom were excluded during the treatment/observation period. Major protocol deviations were recorded for more patients from the bortezomib than from the observational arms (28/186 [15.1%] vs. 9/185 [4.9%]). In the bortezomib arm, main reason to be excluded for major protocol deviation was administration of ≤80% of the total planned dose of bortezomib according to the protocols (22/186 patients; 11.8%). Note: Per-protocol dose reductions or permanent stop of treatment, e.g., protocol-compliant dose reduction due to occurrence of an AE was not considered a major protocol deviation, even if the patient received less than 80% of the originally planned dose. Other major protocol deviations comprised violation of inclusion and exclusion criteria (mostly time from hospital discharge after SCT to date of randomization or patient not in first-line therapy: 8/186 [4.3%] bortezomib vs. 4/185 [2.2%] observation). Four patients of the bortezomib arms were excluded prior to first administration of bortezomib, i.e., did not receive study agent though randomized to bortezomib consolidation therapy. Minor protocol deviations mainly referred to time windows, time from end of pre-treatment to randomization, to health-related parameters such as hypotension, low serum calcium or other clinical laboratory values, and use of excluded medication.

Baseline characteristics:

The two study arms were well comparable regarding demographic data (age, weight, height, BMI, BSA and Karnofsky index as well as general medical history and use of prior medication) in all analysis sets. Age ranged between 35 and 76 years with a mean of 58±9 years (median 59 years). Mean body weight was 77±17 kg (median 76 kg, range 46 to 155 kg) and mean BSA was 1.89±0.22 m^2 (median 1.89 m^2, range 1.39 to 2.9 m^2). The Karnofsky performance status ranged between 60 and 100% with a mean score of 91.6±8.0%. Relevant baseline data are summarized in the following tables.

	Safety Analysis Set (SS)		
	Bortezomib; N=186	**Observation; N=185**	**Total; N=371**
Gender; n (%)			
Male / Female	112 (60.2) / 74 (39.8)	118 (63.8) / 67 (36.2)	230 (62.0) / 141 (38.0)
Age [years]			
n; mean (SD)	186; 58.1 (8.36)	185; 58.0 (8.90)	371; 58.1 (8.62)
Karnofsky performance status [%]			
n; mean (SD)	185; 92.2 (7.57)	182; 91.1 (8.40)	367; 91.6 (8.00)
MM characteristics; n (%)			
State at start of first-line therapy			
IIA /IIB	28 (15.1) / 1 (0.5)	19 (10.3) / 3 (1.6)	47 (12.7) / 4 (1.1)
IIIA /IIIB	133 (71.5) / 20 (10.8)	131 (70.8) / 26 (14.1)	264 (71.2) / 46 (12.4)
Other / Missing	3 (1.6) / 1 (0.5)	4 (2.2) / 2 (1.1)	7 (1.9) / 3 (0.8)
Type of myeloma			
IgG	105 (56.5)	101 (54.6)	206 (55.5)
IgA / Light chains only	40 (21.5) / 39 (21.0)	45 (24.3) / 36 (19.5)	85 (22.9) / 75 (20.2)
IgM / IgD	1 (0.5) / 1 (0.5)	1 (0.5) / 1 (0.5)	2 (0.5) / 2 (0.5)
Type of light chain			
Kappa / lambda	126 (67.7) / 60 (32.3)	128 (69.2) / 56 (30.3)	254 (68.5) / 116 (31.3)
Cytogenetic changes			
Not done / NA	46 (24.7) / 7 (3.8)	47 (25.4) / 7 (3.8)	93 (25.1) / 14 (3.8)
Done, but no change	46 (24.7)	47 (25.4)	93 (25.1)
Changes*	87 (46.8)	83 (44.9)	170 (45.8)
del13q	48 (25.8)	40 (21.6)	88 (23.7)
t(4;14)	11 (5.9)	16 (8.6) / —	27 (7.3) /
del 17p	8 (4.3)	8 (4.3)	16 (4.3)
other	56 (30.1)	50 (27.0)	106 (28.6)
High-Risk 1: del13q, t(4;14) or del17p	52 (28.0)	50 (27.0)	102 (27.5)
High-Risk 2: t(4;14) or del17p	18 (9.7)	23 (12.4)	41 (11.1)

NA = not assessed; * Note: multiple remarks possible: a considerable number of patients had multiple cytogenetic changes

	Safety Analysis Set (SS)		
	Bortezomib; N=186	**Observation; N=185**	**Total; N=371**
MM pre-treatment; n (%)			
Induction therapy			
Bortezomib-naïve[A]	91 (48.9)	94 (50.8)	185 (49.9)
ID / D	24 (12.9) / 23 (12.4)	27 (14.6) / 26 (14.1)	51 (13.7) / 49 (13.2)
VAD / AD	15 (8.1) / 10 (5.4)	19 (10.3) / 13 (7.0)	34 (9.2) / 23 (6.2)
Number of cycles			
1 / 2	11 (12.1) / 14 (15.4)	11 (11.7) / 13 (13.8)	22 (11.9) / 27 (14.6)
3 / 4	19 (20.9) / 31 (34.1)	28 (29.8) / 32 (34.0)	47 (25.4) / 63 (34.1)
5 / 6	1 (1.1) / 3 (3.3)	— / —	1 (0.5) / 3 (1.6)
7 / 8	1 (1.1) / 1 (1.1)	— / —	1 (0.5) / 1 (0.5)
Bortezomib pre-treated[A]	95 (51.1)	91 (49.2)	186 (50.1)
VCD	77 (41.4)	70 (37.8)	147 (39.6)
Number of cycles			
1 / 2	— / 9 (9.5)	4 (4.4) / 3 (3.3)	4 (2.2) / 12 (6.5)
3 / 4	79 (83.2) / 3 (3.2)	75 (82.4) / 6 (6.6)	154 (82.8) / 9 (4.8)
5 / 6 / 7	1 (1.1) / 1 (1.1) / 1 (1.1)	1 (1.1) / 1 (1.1) / 1 (1.1)	2 (1.1) / 2 (1.1) / 2 (1.1)
HD-CT and Stem cell transplantation (SCT)			
Autologous SCT (ASCT)			
First / second ASCT	184 (98.9)[B] / 105 (56.5)	184 (99.5)[B] / 104 (56.5)	368 (99.2)[B] / 209 (56.3)
Allogeneic SCT			
MRD / MURD	1 (0.5) / —	1 (0.5) / 1 (0.5)	2 (0.5) / 1 (0.3)
Response at end of pre-treatment: "best response baseline"; n (%)			
CR / VGPR	44 (23.7) / 58 (31.2)	49 (26.5) / 60 (32.4)	93 (25.1) / 118 (31.8)
PR	64 (34.4)	55 (29.7)	119 (32.1)
MR / NC	5 (2.7) / 3 (1.6)	2 (1.1) / 1 (0.5)	7 (1.9) / 4 (1.1)
ND,NA / Missing	9 (4.8) / 3 (1.6)	16 (8.6) / 2 (1.1)	25 (6.7) / 5 (1.3)

[A] **Note:** only regimens received by ≥10% of patients are included in this summary table; [B] 2 patients missing in bortezomib arms and 1 in observational arms had no data given for performance of ASCT in CRF: ID 52-173(bortezomib) was excluded prior to Day 1 due to neutropenia,IDs 42-2061 (observation) and 43-53 (bortezomib) withdrew consent to study participation;
AD = adriamycin/dexamethasone; D=dexamethasone pulse therapy; ID = idarubicin/dexamethasone; VAD = vincristine/adriamycin/dexamethasone; VCD = bortezomib/cyclophosphamide/dexamethasone; ASCT = autologous stem cell transplantation; M(U)RD = matched (un)related donor; CR = complete response; VGPR = very good partial response; PR = partial response; MR = minimal response; PD = progressive disease

Treatment exposure:

Patients randomized to the bortezomib arms were to receive 4 intravenous (IV) injections of 1.6 mg/m^2 bortezomib during each of 4 cycles in weekly intervals. Median time between administrations is 7 days for all injections in all cycles with means between 7.0 and 7.2 days. Median number of injections is 16 as per protocol with a mean (SD) number of 13.3±4.4 injections (n=182) and a range from 1 to 16. Thus, for the majority of patients administration was according to schedule. Mean total dose administered in n=182 patients randomized to the bortezomib arms was about 38.7±13.5 mg corresponding to a mean relative dose of about 80.3±29.7% in N=186 patients of the SS of the cumulative planned dose of 25.6 mg/m² (1.6 mg/m² x 4 weekly injections x 4 cycles). Mean exposure was about 110±39 days (n=181), with a range from 1 to 155 days. Median total dose was 43.2 mg with a median extent of exposure 127 days.

EFFICACY RESULTS:

- PFS in bortezomib-treated patients was superior with a median PFS of 33.6 months to that in patients under observation with a median PFS of 27.8 months in the primary confirmatory statistical analysis using a Cox proportional hazards regression model controlled for the effect of study group, age, presence of cytogenetic changes, and best response at start of therapy (HR=0.702 with a 95% CI of 0.546 to 0.903; p=0.0058). This was confirmed in analyses of PFS from randomization (HR=0.695, 95% CI 0.541 to 0.894; exploratory p=0.0046) as well as in the PPS analysis and Cox regression analyses using modified variables.

- Similar results were obtained for analyses of EFS and EFS from randomization as well as for TTP and TTP from randomization (longer median of 3.4 months for EFS and longer time to progression of 5.4 months for bortezomib-treated patients).
- In subgroup analyses, benefit of bortezomib treatment was most pronounced for patients with a baseline response of less than VGPR (n=124; median PFS 33.3 vs. 24.5 months; HR=0.583 with p=0.0089). Patients who had achieved a response of VGPR and better after high-dose chemotherapy and stem-cell transplant at baseline, also benefitted from bortezomib consolidation, however to a lesser extent and the difference observed did not reach statistical significance. Patients receiving bortezomib showed a median PFS of 33.4 months compared to 29.3 months for patients under observation (n=206; HR=0.813 with p=0.2179)
- Subgroup analyses of patients with high-risk cytogenetic changes also pointed to a benefit for bortezomib-treated patients, however, statistical significance in terms of exploratory p-values ≤0.05 was not reached, most likely due to the small sample size. Patients with high-risk cytogenetic changes defined by presence of del13q, t(4;14) or del17p were more likely to have PFS until end of evaluation under bortezomib as compared to observation (n=98; median PFS 30.6 vs. 24.2 months; HR=0.657 with p=0.0738). Alternatively defined high-risk cytogenetic changes of t(4;14) or del17p were observed in a total of 37 patients (17 bortezomib-treated, 20 under observation). Of these, all patients randomized to observation suffered from disease progression or died during follow-up, with a median follow-up of 42 months after randomization. In contrast, 4/17 patients under bortezomib treatment survived without progression (HR=0.629; 95% CI 0.312 to 1.270; p=0.1898).
- OS and OS from randomization were similar in bortezomib-treated and observed patients (HR=0.939; 95% CI 0.635 to 1.390, p=0.7535) with immature follow-up (102/357 (28.6%) patients died, 47 (26.6%) in the bortezomib arm and 55 (30.6%) in the observation arm). As expected, exploratory p was >0.05 for these analyses, ie, statistical significance could not be demonstrated. Similarly, no statistical significance was reached for an additional analysis of post-progression survival.
- More bortezomib-treated patients than patients under observation had reached a response of VGPR or better at the EoT Concluding Visit (61.6% bortezomib vs. 47.8% observation). Clearly more patients improved their depth of response under bortezomib from less than VGPR to VGPR or CR in the bortezomib arm (27/177 patients, 15.3%) than in the observation arm (13/180 patients, 7.2%).
- In QoL assessments, no relevant difference was observed regarding overall state of health when comparing patients of the bortezomib and the observational arms regarding EQ-5D VAS. Most prominent among reported problems was pain / discomfort in patients of both arms throughout the studies. The percentage of patients reporting problems in EQ-5D regarding mobility, self-care, usual activities and anxiety/depression declined throughout the study in patients of both arms. No clinically meaningful differences were observed at any time throughout the study. In QLQ-C30, no clinically meaningful differences were observed when comparing mean ratings of bortezomib-treated patients and patients under observation regarding assessment of fatigue, dyspnea, insomnia and general functioning scores. Mean ratings of patients under bortezomib treatment increased for several gastrointestinal symptoms during bortezomib treatment (nausea / vomiting, diarrhea and constipation). Mean ratings of appetite loss and pain also were higher in bortezomib-treated patients.
- The total number of SREs was slightly lower in bortezomib-treated patients both at EoT Concluding Visit and during post-treatment follow-up (SREs until EoT in 1.7% vs. 3.3% and during follow-up in 24.9% vs. 28.3% of patients). Mean and median time to occurrence of an SRE were nearly the same in both study arms (about 25 months).

The results of main analyses are summarized in the following tables.

ES; N=357: Survival and progression	Bortezomib; n=177	Observation; n=180
Primary variable: PFS from start of first-line therapy; data source: **Tables C.4.1.1.1 / C.4.1.2**		
n (%) patients censored: survival, no progression	66 (37.29)	37 (20.56)
PFS [months] median (95% CI)	33.60 (30.13 to 36.73)	27.80 (24.17 to 32.23)
Cox proportional hazard: p	0.0058	
Cox proportional hazard: HR (95% CI)	0.702 (0.546 to 0.903)	
PFS from randomization; data source: **Tables C.4.1.4.1 / C.4.1.5**		
n (%) patients censored: survival, no progression	66 (37.29)	37 (20.56)
PFS [months] median (95% CI)	23.07 (19.33 to 27.37)	17.20 (13.77 to 21.43)
Cox proportional hazard: p	0.0046	
Cox proportional hazard: HR (95% CI)	0.695 (0.541 to 0.894)	
EFS from start of first-line therapy; data source: **Tables C.4.2.1.1.1 / C.4.2.1.2**		
n (%) patients censored: survival, no event	73 (41.24)	50 (27.78)
EFS [months] median (95% CI)	37.77 (35.27 to 43.30)	34.27 (29.97 to 38.77)
Cox proportional hazard: p	0.0244	
Cox proportional hazard: HR (95% CI)	0.741 (0.571 to 0.962)	
EFS from randomization; data source: **Table C.4.2.1.4.1**		
Cox proportional hazard: p	0.0196	
Cox proportional hazard: HR (95% CI)	0.733 (0.565 to 0.952)	
OS from start of first-line therapy; data source: **Tables C.4.2.3.1.1 / C.4.2.3.2**		
n (%) patients censored: survival	130 (73.45)	125 (69.44)
Survival time [months] median	not reached	not reached
Cox proportional hazard: p	0.7535	
Cox proportional hazard: HR (95% CI)	0.939 (0.635 to 1.390)	
OS from randomization; data source: **Table C.4.2.3.4.1**		
Cox proportional hazard: p	0.7643	
Cox proportional hazard: HR (95% CI)	0.942 (0.637 to 1.394)	
OS from start of first-line therapy to start of new chemotherapy; data source: **Tables C.4.2.3.4**		
n (%) patients censored: survival	130 (73.45)	125 (69.44)
Survival time [months] median	64.77	64.50
Cox proportional hazard, univariate analysis: p	0.5858	
Cox proportional hazard, univariate analysis: HR (95% CI)	0.897 (0.608 to 1.326)	
TTP from start of first-line therapy; data source: **Tables C.4.2.4.1.1 / C.4.2.4.2**		
n (%) patients censored: TTP longer than assessment period	67 (37.85)	39 (21.67)
TTP [months] median (95% CI)	33.60 (30.13 to 37.30)	28.17 (24.17 to 32.70)
Cox proportional hazard: p	0.0071	
Cox proportional hazard: HR (95% CI)	0.707 (0.549 to 0.910)	
TTP from randomization; data source: **Tables C.4.2.4.4.1 / C.4.2.4.5**		
n (%) patients censored: TTP longer than assessment period	67 (37.85)	39 (21.67)
TTP [months] median (95% CI)	23.10 (19.33 to 28.00)	17.27 (13.80 to 21.47)
Cox proportional hazard: p	0.0057	
Cox proportional hazard: HR (95% CI)	0.700 (0.544 to 0.902)	
Post-progression survival from start of first-line therapy; data source: **Table C.4.2.8.1.1**		
Cox proportional hazard: p	0.1546	
Cox proportional hazard: HR (95% CI)	1.342 (0.895 to 2.011)	

Cox proportional hazard controlled for the effect of study group (bortezomib vs. observation), age (>60 vs. ≤60 years), presence of cytogenetic changes ("not done", "del13q / t:[4;14] / del17p" and "other" vs. "no change"), and best response at start of therapy ("PR" and "MR / NC from MR" vs. "CR+VGPR"); ES = efficacy analysis set; CI = confidence interval; HR = hazard ratio; PFS / EFS / OS = progression-free / event-free / overall survival; TTP = time to progression

ES; N=357: response, QoL and SREs	Bortezomib; n=177	Observation; n=180
Best response at Concluding Visit: n (%); data source: **Tables C.4.2.2.1 / C.4.2.2.2 / C.4.2.2.3**		
≥VGPR	109 (61.6)	86 (47.8)
PR	37 (20.9)	48 (26.7)
MR / NC	4 (2.3) / 3 (1.7)	1 (0.6) / 5 (2.8)
Missing	24 (13.6)	40 (22.2)
Improvement from less than VGPR to ≥ VGPR	27 (15.3)	13 (7.2)
Worsening from ≥ VGPR to less than VGPR	10 (5.6)	14 (7.8)
QoL: n (%); data source: **Table C.4.2.5.2**		
EQ-5D; VAS: higher values indicate a better state of health		
Day 1: Cycle 1: n; mean (SD)	155; 72.9 (17.2)	158; 72.3 (16.9)
EoT Concluding Visit: n; Mean (SD)	144; 75.6 (17.5)	154; 74.4 (18.3)
Follow-up, Month 12: n; Mean (SD)	90; 74.3 (19.5)	87; 74.5 (19.3)
Change of VAS from baseline (Day 1)		
EoT Concluding Visit: n; mean (SD)	132; 2.6 (13.1)	141; 2.6 (14.1)
Follow-up, Month 12: n; mean (SD)	79; 1.0 (15.2)	85; 0.8 (17.6)
QLQ-C30; global state of health: higher values indicate a better state of health; data source**: Table C.4.2.5.3**		
Day 1: Cycle 1: n; mean (SD)	163; 68.3 (19.1)	161; 66.5 (18.5)
EoT Concluding Visit: n; mean (SD)	147; 69.2 (19.7)	156; 68.4 (20.8)
Follow-up, Month 12: n; mean (SD)	87; 67.1 (23.2)	86; 68.1 (22.2)
Change of QLQ-C30 global health status from baseline (Day 1)		
EoT Concluding Visit: n; mean (SD)	141; 0.7 (17.6)	142; 1.3 (19.0)
Follow-up, Month 12: n; mean (SD)	82; –2.2 (19.0)	83; –0.1 (22.6)
Occurrence of SREs: n (%); data source: **Table C.4.2.6**		
Recorded at EoT (total)	3 (1.7)	6 (3.3)
During post-treatment follow-up (total)	44 (24.9)	51 (28.3)
Time to occurrence of SREs; data source: **Table C.4.2.7**		
N	44	48
Mean (SD)	25.10 (12.501)	25.86 (14.338)

ES = efficacy analysis set; SD = standard deviation; QoL = quality of life; re. = remark; VAS = visual analogue scale; SRE = skeletal-related event

SAFETY RESULTS:

TEAEs were reported in 177/186 bortezomib-treated patients (95.2%) and 174/185 patients under observation (94.1%).

Drug-related TEAEs occurring with an incidence of ≥10% in bortezomib-treated patients are summarized in the following table sorted by frequency. The majority of drug-related TEAEs were assessed as possibly related. Highest relationship to bortezomib treatment of very likely was documented for 46/186 patients (24.7%), highest relationship probable for 62/186 (33.3%) and possible for 58/186 (31.2%). Most common TEAEs with very likely relationship were “gastrointestinal disorders” (occurring in 10.8%). Most common TEAEs in total concerned “infections and infestations” (reported in 62.3% of patients, overall), “gastrointestinal disorders” (43.9% of patients, overall), “musculoskeletal and connective tissue disorders” (43.7% of patients, overall) and “general disorders and administration site conditions” (42% of patients, overall).

Adverse event incidences	n (%) Bortezomib; N=186	Observation; N=185	Total; N=371
Patients with AEs	181 (97.3)	175 (94.6)	356 (96.0)
Patients with NTEAEs	43 (23.1)	33 (17.8)	76 (20.5)
Patients with SAEs	25 (13.4)	34 (18.4)	59 (15.9)
Patients with NTESAEs	6 (3.2)	6 (3.2)	12 (3.2)
Patients with TEAEs	177 (95.2)	174 (94.1)	351 (94.6)
Difference: %n bort – %n obs (95% CI)*	1.1 (–3.5 to 5.7)		
Patients with TESAEs	20 (10.8)	31 (16.8)	51 (13.7)
Difference: %n bort – %n obs (95% CI)*	–6.0 (–13.0 to 1.0)		
Premature discontinuation due to TEAE	28 (15.1)		28 (7.5)
Premature discontinuation due to TESAE	8 (4.3)		8 (2.2)
Patients who died	47 (25.3)	56 (30.3)	103 (27.8)

AE = adverse event, TEAE = treatment-emergent adverse event, NTEAE = non-treatment-emergent adverse event; CI = confidence interval; * difference in incidence calculated as $n\%_{bortezomib}$ minus $n\%_{observation}$ of patients with TEAEs

Primary SOC / PT	n (%) Bortezomib; N=186	Observation; N=185	Total; N=371
Total	177 (95.2)	174 (94.1)	351 (94.6)
Infections and infestations	121 (65.1)	110 (59.5)	231 (62.3)
Nasopharyngitis	44 (23.7)	50 (27.0)	94 (25.3)
Herpes zoster	32 (17.2)	16 (8.6)	48 (12.9)
Bronchitis	7 (3.8)	19 (10.3)	26 (7.0)
Gastrointestinal disorders	**110 (59.1)**	**53 (28.6)**	163 (43.9)
Diarrhea	**79 (42.5)**	**15 (8.1)**	94 (25.3)
Nausea	**62 (33.3)**	**9 (4.9)**	71 (19.1)
Vomiting	**51 (27.4)**	**6 (3.2)**	57 (15.4)
Constipation	22 (11.8)	5 (2.7)	27 (7.3)
Musculoskeletal and connective tissue disorders	85 (45.7)	77 (41.6)	162 (43.7)
Back pain	32 (17.2)	32 (17.3)	64 (17.3)
Bone pain	19 (10.2)	9 (4.9)	28 (7.5)
Pain in extremity	20 (10.8)	7 (3.8)	27 (7.3)
General disorders and administration site cond.	**98 (52.7)**	**58 (31.4)**	156 (42.0)
Fatigue	**45 (24.2)**	**17 (9.2)**	62 (16.7)
Pyrexia	29 (15.6)	16 (8.6)	44 (11.9)
Asthenia	19 (10.2)	6 (3.2)	25 (6.7)
Nervous system disorders	**90 (48.4)**	**48 (25.9)**	138 (37.2)
Polyneuropathy	30 (16.1)	12 (6.5)	42 (11.3)
Paraesthesia	25 (13.4)	9 (4.9)	34 (9.2)
Headache	22 (11.8)	5 (2.7)	27 (7.3)
Skin and subcutaneous tissue disorders	49 (26.3)	43 (23.2)	92 (24.8)
Respiratory, thoracic and mediastinal dis.	**51 (27.4)**	**31 (16.8)**	82 (22.1)
Cough	29 (15.6)	17 (9.2)	46 (12.4)
Blood and lymphatic system disorders	**52 (28.0)**	**24 (13.0)**	76 (20.5)
Thrombocytopenia	**31 (16.7)**	**10 (5.4)**	41 (11.1)
Leukopenia	**28 (15.1)**	**10 (5.4)**	38 (10.2)
Investigations	29 (15.6)	36 (19.5)	65 (17.5)
Neoplasms benign, malignant and unspecified	**16 (8.6)**	**36 (19.5)**	52 (14.0)
Multiple myeloma	**13 (7.0)**	**34 (18.4)**	47 (12.7)
Metabolism and nutrition disorders	27 (14.5)	14 (7.6)	41 (11.1)
Vascular disorders	22 (11.8)	13 (7.0)	35 (9.4)
Eye disorders	**26 (14.0)**	**6 (3.2)**	32 (8.6)

SOC = system organ class; PT = preferred term; dis. = disorders, cond. = conditions; sorted by decreasing total incidence; SOCs/PTs with ≥10% difference in incidence between bortezomib and observation printed in bold type

TEAEs occurring with a difference of incidences in both arms of ≥10% concern "neoplasms, benign, malignant and unspecified" (apart from one case of breast cancer all multiple myeloma) which were reported more often in patients under observation. TEAEs occurring with a higher incidence in bortezomib-treated patients refer to "gastrointestinal disorders" (diarrhea, nausea and vomiting), "general disorders and administration site conditions" (fatigue), "nervous system disorders", "respiratory, thoracic and mediastinal disorders", "blood and lymphatic system disorders" (thrombocytopenia, leukopenia) and "eye disorders". Other TEAEs occurring more often in bortezomib-treated patients are polyneuropathy, paraesthesia, headache, herpes zoster and pain in extremity. Generally, these observations correspond well to data on concomitant medication and problems reported in QoL questionnaires.

(TE)SAEs

SAEs occurred in 15.9% of patients, overall, with a higher incidence in patients under observation (25/186 [13.4%] bortezomib-treated vs. 34/185 [18.4%] patients under observation). Most of these were treatment-emergent, i.e., were reported during the treatment/observation period. TESAEs occurred in 20/186 bortezomib-treated patients (10.8%; 30 events) and 31/185 patients under observation (16.8%; 46 events including 4 deaths; difference $n\%_{bort.}$ minus $n\%_{obs.} = –6\%$). 17 of the 30 TESAEs occurring in bortezomib-treated patients were at least possibly related to the study agent (10 possibly, 6 probably and 1 very likely related). Relationship to bortezomib was not related or doubtful for TESAEs occurring in 6 bortezomib-treated patients, it was assessed as possible in 8, probable in 5 and very likely in 1 patient, only. Most common PTs in bortezomib-treated patients refer to infections, general disorders, namely pyrexia, and gastrointestinal disorders. This is in-line with the known safety profile of bortezomib. Overall, most TESAEs were not assessed as drug-related, very likely relationship occurred for herpes zoster ophthalmic in 1/186 patients (0.5%) only. Worst toxicity severe was rated for TESAEs in 4 patients (pneumonia, sepsis, diarrhea and vomiting in 1/186 [0.5%] patients each). No new and unexpected safety concerns were identified. This conclusion is also confirmed by evaluation of TEAEs of specific interest, namely events relating to PNP, infections in general and herpes zoster infection specifically. Most common PTs in patients under observation refer to infections (mainly herpes zoster) and MM.

TEAEs leading to premature discontinuation

TEAEs leading to premature discontinuation of bortezomib treatment occurred in 28/186 (15.1%) patients of the bortezomib arms. They refer mostly to "gastrointestinal disorders", "general disorders and administration site conditions", "infections and infestations" and "nervous system disorders". TEAEs leading to discontinuation and occurring in more than 1 bortezomib-treated patient comprise nausea, diarrhea and vomiting, polyneuropathy and multiple myeloma, pyrexia and herpes zoster and asthenia. 8/186 patients experienced TESAEs leading to premature discontinuation, four of them herpes zoster infections and one patient suffering from pneumonia.

Deaths

Death was reported in 47/186 bortezomib-treated patients (25.3%) and 56/185 patients under observation (30.3%) during the post-observation period. Reason stated was study indication, i.e., MM for the majority of these patients. "Other" reasons nearly all reflect life-threatening conditions resulting from the study indication or are associated with previous treatment (SCT). Relationship to bortezomib was assessed as not related for nearly all deaths. It was doubtful for 2 patients overall, only (reason for death was study indication in ID 18-152 and sepsis in ID 22-24). SAEs with outcome death were reported for 1 bortezomib-treated patient (reason for death was study indication with term 'MM' on SAE form) and 6 patients under observation (reasons for death was study indication with the terms 'acute GVHD in skin', 'renal failure acute', 'sepsis' and 'MM' in 1 patient each). 'Pneumonia primary atypical' was the reason for death on SAE form in ID 7-2105 and 'other' with verbatim term 'MM' in ID 32.69.

- **Note:** The reason for death had to be entered by ticking either 'study indication' (indicating multiple myeloma) or 'other'. In case of 'other', reason had to be specified. Rating occurred according to investigators' assessment. This gave rise to a number of discrepancies due to the fact that MM may lead to several serious and life-threatening conditions, which in themselves are a sufficient reason for death. Therefore, reason occasionally was given as "study indication" in the CRF, while on the pertaining SAE form another verbatim description was given.

TEAEs of specific interest

Peripheral neuropathies NES occurred in 4 bortezomib-treated patients. Selected PNPs occurred in 30/186 bortezomib-treated vs 12/185 (6.5%) patients under observation. Most observed neuropathies were mild to moderate, 5 patients in the bortezomib arm and no patient in the observation arm suffered from grade 3 neuropathy. Non-serious grade 4 neuropathies or serious PNP-related TEAEs were not reported.

	n (%)		
Primary SOC / PT*	**Bortezomib; N=186**	**Observation; N=185**	**Total; N=371**
Selected PNPs	34 (18.3)	12 (6.5)	46 (12.4)
Polyneuropathy	30 (16.1)	12 (6.5)	42 (11.3)
Neuropathy peripheral	3 (1.6)	—	3 (0.8)
Peripheral sensory neuropathy	1 (0.5)	—	1 (0.3)
Peripheral neuropathies NEC	4 (2.2)	—	4 (1.1)
Neuropathy peripheral	3 (1.6)	—	3 (0.8)
Peripheral sensory neuropathy	1 (0.5)	—	1 (0.3)

* bort. = bortezomib pre-treated / -naïve refers to regimen of first-line induction therapy; PTs sorted by total decreasing frequency; SOC = system organ class; PT = preferred term

Infection-related TEAEs occurred in 152/186 bortezomib-treated patients (81.7%) and 120/185 (64.9%) patients under observation. Apart from “infections and infestations” occurring in 119/186 bortezomib-treated patients (64%) and 104/186 (56.2%) patients under observation, infection-related TEAEs mainly relate to SOCs “gastrointestinal disorders” (mainly diarrhea in 79/186 bortezomib-treated patients [42.5%] vs. 15/185 [8.1%] patients under observation) and “general disorders and administration site conditions”(mainly pyrexia in 27/186 bortezomib-treated patients [14.5%] vs. 16/185 [8.6%] patients under observation). Most common “infections and infestations” are nasopharyngitis, herpes zoster and bronchitis. Herpes zoster infections occurred clearly more often in bortezomib-treated patients (17.6% vs. 8.6%), bronchitis more often in patients under observation (3.8% bortezomib vs. 10.3% observation). In 5 patients of the observational arms and in 2 bortezomib-treated patients they were rated as severe (observation: 2 cases each of herpes zoster infection and appendicitis and one case of sepsis; bortezomib-treated patients: one patient with pneumonia and one with sepsis).

In total, herpes zoster-related TEAEs were documented in 33/186 bortezomib-treated patients (17.7%) and 17/185 (9.2%) patients under observation. The incidence of non-serious TEAEs as well as TESAEs related to herpes zoster infection was clearly higher in bortezomib-treated patients (occurring in 29/186 [15.6%] vs.12/185 [6.5%]). Herpes zoster-related TESAEs occurred in bortezomib-treated and observed patients with the same frequency (3.8%). Non-serious herpes zoster-related TEAEs were of severe intensity in 4/186 bortezomib-treated patients (2.2%) vs. 2/185 (1.1%) patients under observation. In total 8 patients experienced herpes zoster infections even though they received aciclovir prophylaxis (6 bortezomib-treated and 2 under observation). The majority of patients with herpes zoster-related TEAEs had not received aciclovir prophylaxis (42 in total, 27 bortezomib-treated and 15 under observation).

Other safety parameters

No relevant safety observations were reported regarding clinical laboratory values, vital signs, physical examinations, electrocardiograms and additional measurements, especially when considering relationship to bortezomib treatment.

STUDY LIMITATIONS:

A limitation of the present studies is the impaired interpretability of OS data which is due to limited follow-up as well as lacking information on regimen of MM treatment following progression, i.e., during the post-observation period. Thus, it cannot be ruled out that a considerable number of patients may then have received bortezomib-containing regimens, especially those of the observational arms previously untreated with bortezomib. It is therefore not possible to clearly distinguish between bortezomib-treated and –untreated patients in the post-observation period.

CONCLUSION(S):

- Main objective of the present study was to demonstrate superiority of bortezomib consolidation treatment over observation by evaluation of the primary endpoint PFS defined as progression-free survival from the first day of administration of the first myeloma-specific chemotherapy to progression/relapse or to death. Demonstration of superiority in Cox proportional hazards regression analysis controlled for the effect of study group, age, presence of cytogenetic changes, and best response prior to start of consolidation therapy was achieved with p=0.0053 clearly below the adjusted level of significance of 0.04023.
- Bortezomib consolidation treatment prolonged PFS by about 6 months in the present studies. This was corroborated by analysis of PFS from randomization.
- Response rates improved following bortezomib consolidation therapy (improvement to ≥ VGPR in 15% of patients compared to 7% of patients in the observation arm) and more bortezomib-treated patients reached a response of ≥VGPR than patients under observation (62% versus 48%).
- Patients with a baseline response of <VGPR (ie, PR, MR or NC from MR) appeared to benefit the most from bortezomib treatment with a median PFS time of nearly 9 months longer than patients randomized to observation (corresponding exploratory p-value of 0.0089).
- Presence of high-risk cytogenetic changes, especially of del13q, t(4;14), and del17p mutations, was confirmed as risk factor for worse prognosis. When comparing bortezomib-treated vs. patients under observation, median PFS was about 34 vs. 30 months in patients with normal karyotype and about 31 vs. 24 months in patients with cytogenetic changes del13q, t(4;14) or del17p. Noteworthy, bortezomib consolidation appeared to overcome adverse prognosis associated with these high-risk cytogenetic changes, i.e., bortezomib consolidation therapy achieved similar PFS benefits in patients with high-risk cytogenetic changes del13q, t(4;14) or del17p as compared to normal karyotypes. Median PFS time was about 7 months longer under bortezomib treatment for patients with del13q, t(4;14) or del17p mutations. A protective effect is also seen when specifically analyzing results of patients with an alternative definition of high-risk disease, carrying mutations t(4;14) or del17p. Of overall 38 patients with these high-risk mutations, 4 survived to the end of the studies under bortezomib-treatment, while all patients randomized to observation died. Median PFS time was 4.5 months longer for these later patients with high-risk cytogenetic changes t(4;14) or del17p under bortezomib treatment. However, it should be noted that the absolute number of patients in this subgroup is very small and results lack statistical significance.
- Similar results were obtained for analyses of EFS and EFS from randomization compared to PFS, supporting the overall benefit of bortezomib consolidation: bortezomib-treated patients had a 3.5 months longer median event-free survival.
- Furthermore, TTP was 5.4 months longer for bortezomib-treated patients.
- Follow-up was insufficient to allow any strong conclusion with regard to overall survival. With a median follow-up of 51 months from first antimyeloma treatment given, similar OS rates were observed with median OS not reached in either study arm. Post-progression survival has been analyzed post-hoc to supplement overall survival data. Given the limitations of insufficient follow-up no statistical significant difference in an exploratory sense was shown. Unfortunately data on subsequent therapies was not collected, which further limits the interpretation of this analysis.
- Observations reported in QoL questionnaires correspond well to use of concomitant medication and documented (TE)AEs. Overall, state of health did not differ relevantly between arms, highlighting the good tolerability of bortezomib consolidation in this study. Most prominent among reported problems was pain / discomfort in patients of both arms throughout the studies.

- A small number of SREs were observed during the studies. The total number of SREs was lower in bortezomib-treated patients both at the Concluding Visit and during the post-treatment period. Mean and median time to occurrence of an SRE were nearly the same in both study arms.
- Safety in bortezomib-treated patients overall was similiar to the safety in patients under observation. Incidence of TEAEs was about the same in both arms. TEAEs occurring more often in bortezomib-treated patients related to gastrointestinal disorders (diarrhea, nausea and vomiting) and herpes zoster reactivation, as well as fatigue, cough, thrombocytopenia, leukopenia and eye disorders. This reflects the known safety profile of bortezomib.
- All deaths occurred during the post-observation period (103, in total). Nearly all were assessed as due to MM or were due to life-threatening conditions resulting from the study indication or were associated with previous treatment (SCT). Death of 2 patients was assessed as doubtfully related to treatment (one due to MM and one due to sepsis), for all other patients who died relationship to bortezomib was “not related”.
- No new and unexpected safety concerns were identified. This conclusion is also confirmed by evaluation of TEAEs of specific interest, namely events relating to PNP, infections in general and herpes zoster infection specifically.

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