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Randomised phase II study to optimise melphalan, prednisolone, and bortezomib in untreated multiple myeloma (JCOG1105)

Dai Maruyama,[1] Shinsuke Iida,[2] Gakuto Ogawa,[3] Noriko Fukuhara,[4] Sachiko Seo,[5] Kana Miyazaki,[6] Makoto Yoshimitsu,[7] Junya Kuroda,[8] Norifumi Tsukamoto,[9] Hideki Tsujimura,[10] Akira Hangaishi,[11] Takahiro Yamauchi,[12] Takahiko Utsumi,[13] Ishikazu Mizuno,[14] Yasushi Takamatsu,[15] Yasuyuki Nagata,[16] Koichiro Minauchi,[17] Eiichi Ohtsuka,[18] Ichiro Hanamura,[19] Shinichiro Yoshida,[20] Satoshi Yamasaki,[21] Youko Suehiro,[22] Yutaro Kamiyama,[23] Kunihiro Tsukasaki[24] and Hirokazu Nagai[25]

[1]*Department of Hematology, National Cancer Center Hospital, Tokyo,* [2]*Department of Hematology and Oncology, Nagoya City University Hospital, Nagoya,* [3]*JCOG Data Center/Operating Office, National Cancer Center Hospital, Tokyo,* [4]*Department of Hematology and Rheumatology, Tohoku University Hospital, Sendai,* [5]*Department of Hematology, National Cancer Center Hospital East, Kashiwa,* [6]*Department of Hematology and Oncology, Mie University School of Medicine, Tsu,* [7]*Department of Hematology and Rheumatology, Kagoshima University Hospital, Kagoshima,* [8]*Division of Hematology and Oncology, Kyoto Prefectural University of Medicine, Kyoto,* [9]*Department of Hematology, Gunma University, Maebashi,* [10]*Division of Hematology-Oncology, Chiba Cancer Center, Chiba,* [11]*Division of Hematology, NTT Medical Center Tokyo, Tokyo,* [12]*Department of Hematology and Oncology, University of Fukui Hospital, Fukui,* [13]*Department of Hematology, Shiga General Hospital, Moriyama,* [14]*Division of Hematology, Hyogo Cancer Center, Akashi,* [15]*Division of Medical Oncology,*

Summary

We conducted a randomised phase II study to determine the optimal dose and schedule of melphalan, prednisone, and bortezomib (MPB) (jRCTs031180097). Transplant-ineligible untreated multiple myeloma patients were randomised to Arm A (twice weekly bortezomib in one six-week cycle followed by eight five-week cycles of four times once weekly bortezomib with melphalan and prednisolone on days 1–4) or Arm B (nine four-week cycles of three times once weekly bortezomib with melphalan and prednisolone on days 1–4). The primary end-point was complete response (CR) rate. Of 91 patients randomised to two arms, 88 were eligible. The median cumulative bortezomib doses were 45·8 and 35·1 mg/m^2, CR rate was 18·6% [95% confidence interval (CI) 8·4–33·4] and 6·7% (95% CI 1·4–18·3), and the median progression-free survival (PFS) was 2·5 and 1·4 years in Arms A and B [hazard ratio (HR) 1·93 (95% CI 1·09–3·42)], respectively. Frequent grade ≥3 haematologic toxicities in Arms A and B were neutropenia (64·4% vs. 28·3%) and thrombocytopenia (35·6% vs. 10·9%). Grade 2/3 peripheral neuropathy was observed in 24·4/2·2% in Arm A and 8·7/0% in Arm B. In conclusion, Arm A was the more promising regimen, suggesting that the twice weekly schedule of bortezomib in the first cycle and higher cumulative dose of both bortezomib and melphalan influences the efficacy of modified MPB.

Keywords: multiple myeloma, eldery, clinical studies.

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Hematology and Infectious Diseases, Fukuoka University Hospital, Fukuoka, [16]Department of Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu, [17]Department of Hematology, Sapporo Hokuyu Hospital, Sapporo, [18]Department of Hematology, Oita Prefectural Hospital, Oita, [19]Division of Hematology, Aichi Medical University, Nagakute, [20]Department of Hematology, National Hospital Organization Nagasaki Medical Center, Ohmura, [21]Department of Hematology and Clinical Research Institute, National Hospital Organization Kyushu Medical Center, [22]Department of Hematology, National Hospital Organization Kyushu Cancer Center, Fukuoka, [23]Department of Clinical Oncology and Hematology, The Jikei University Hospital, Tokyo, [24]Department of Hematology, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Saitama, and [25]Department of Hematology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

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Correspondence: Dai Maruyama, Department of Hematology, National Cancer Center Hospital, Tokyo, Japan.
E-mail: dmaruyam@ncc.go.jp

Introduction

The melphalan, prednisolone plus bortezomib (MPB) regimen was established as a standard of care for patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM) in a randomised phase III study comparing MPB with melphalan plus prednisolone (MP) (VISTA study).[1] The VISTA employed an original MPB regimen comprising four six-week cycles of twice weekly bortezomib administration, followed by five six-week cycles of once weekly bortezomib; no maintenance therapy was administered after completing these nine cycles. However, this 'intensive' MPB schedule was associated with several notable adverse events including peripheral neuropathy, gastrointestinal symptoms, and haematologic toxicities. For example, in a Japanese phase I/II study of 'intensive' MPB therapy for NDMM, the median number of treatment cycles administered was 4·5 and only 32% of patients completed the treatment, mainly because of adverse events.[2] Therefore, we sought to improve the tolerability of the MPB regimen through a well-designed clinical trial.

In the PETHEMA/GEM05 study, a less intensive modified MPB regimen comprising one six-week cycle of twice weekly bortezomib administration followed by five five-week cycles of once weekly bortezomib dosing was evaluated.[3] Similarly, the GIMEMA MM-03-05 study initially used the VISTA MPB protocol; however, it was amended to a less intensive modified MPB regimen comprising nine five-week cycles of once weekly bortezomib administration to reduce the incidence of peripheral neuropathy.[4,5] Both modified MPB regimens improved the tolerability without compromising the efficacy. The cumulative dose of bortezomib may play an important role in its efficacy.[6] However, because there have been no randomised trials, the optimal dosing schedule of the modified MPB regimen and the impact of cumulative bortezomib dose on outcomes in patients with transplant-ineligible NDMM remain unclear. Therefore, the objective of this randomised phase II study, Japan Clinical Oncology

Group (JCOG)1105, was to compare two less intensive modified MPB regimens for selecting a more optimal regimen in transplant-ineligible NDMM.

Patients and methods

Trial information

This open-label randomised phase II multicentre trial (JCOG1105, jRCTs031180097) was conducted by the Lymphoma Study Group (LSG) of JCOG. The study protocol was approved by the Protocol Review Committee of JCOG and the respective institutional review boards. Written informed consent was obtained from all patients before enrolment in accordance with the policies of JCOG and the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

Patients

Key eligibility criteria were as follows: (i) diagnosed to have symptomatic multiple myeloma according to the International Myeloma Working Group (IMWG) criteria (2003);[7] (ii) aged 65 to 79 years, or 20 to 64 years for those who are not candidates for high-dose chemotherapy/autologous stem cell transplantation; (iii) previously untreated; (iv) having measurable paraprotein; (v) having neither cardiac amyloidosis nor gastrointestinal amyloidosis; (vi) Eastern Cooperative Oncology Group (ECOG) performance status: 0–2, or 3 due to osteolytic lesions alone; (vii) preserved bone marrow and organ functions; (viii) peripheral neuropathy of grade 1 or less and no neuralgia; and (ix) written informed consent by the patient. Details on eligibility and exclusion criteria are provided in the Supplementary Data S1.

Randomisation and monitoring

Patients were randomly assigned at a 1:1 ratio to Arm A (less intensive, known as PETHEMA/GEM05 MPB) or Arm B (further less intensive MPB) at the JCOG Data Center, using the minimisation method with biased-coin assignment balancing on institution, age (≤64 or ≥65 years), and International Staging System (ISS) stage (I, II or III). Patient information was collected and managed at the JCOG Data Center. The monitoring reports were submitted to and reviewed by the Data and Safety Monitoring Committee of JCOG semi-annually.

Procedures

The study schema is shown in Fig 1. Arm A consisted of one cycle of subcutaneous (SC) or intravenous (IV) bortezomib at 1·3 mg/m^2 administered twice weekly plus 9 mg/m^2 of oral melphalan and 60 mg/m^2 of prednisolone on days 1–4 of a six-week cycle, followed by eight five-week cycles of four times once weekly bortezomib plus the same doses of MP. Arm B consisted of nine four-week cycles of SC or IV bortezomib at 1·3 mg/m^2 administered three times once weekly plus 7 mg/m^2 of melphalan and 60 mg/m^2 of oral prednisolone on days 1–4. Outline of dose modifications is shown in Tables SII–SV and Figure S1.

Treatment responses were assessed according to the IMWG criteria.[8] Response was evaluated at the beginning of each cycle and the end of the treatment. Adverse events (AEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events version 4·0. Chromosomal translocations, t(4;14)(p16;q32) and t(14;16)(q32;q23), which overexpress *FGFR3* and *MAF* mRNA, respectively, were categorised to the high-risk group.[9,10] In contrast, those expressing neither *FGFR3* nor *MAF* mRNA were

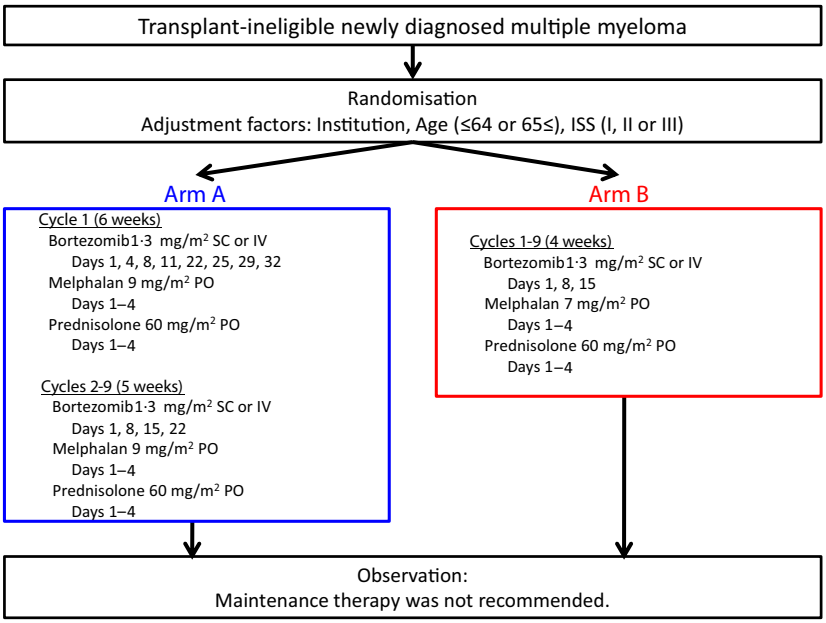

Figure 1. Study Schema. Patients were randomly assigned at 1:1 ratio to Arm A [less intensive, known as PETHEMA/GEM05 melphalan, prednisolone, and bortezomib (MPB)] or Arm B (further less intensive MPB) at the JCOG Data Center, using the minimisation method with biased-coin assignment balancing on institution, age (≤64 or 65 ≤years) and ISS stage (I, II or III).

categorised as the standard-risk group. The expression levels of *CCND1*, *FGFR3*, and *MAF* mRNAs as well as *ACTB* (internal control) were analysed by global real-time quantitative polymerase chain reaction (qRT-PCR) as described previously.[11,12]

Acyclovir and trimethoprim–sulfamethoxazole were recommended as prophylactic medications for all patients to prevent the development of varicella zoster virus and *Pneumocystis jirovecii* pneumonia. In patients with resolved hepatitis B virus (HBV) infection defined as seronegative for hepatitis B surface (HBs) antigen and seropositive for anti-HBc (HB core) or anti-HBs antibodies, a pre-emptive antiviral approach using entecavir was carried out to prevent HBV-related hepatitis, guided by HBV DNA monitoring.[13]

End-points and statistical considerations

The primary end-point was the complete response rate [CR rate, defined as the proportion of CR or stringent CR (sCR) patients] based on the IMWG Uniform Response Criteria.[8] Secondary end-points included overall response rate (ORR), sCR rate, progression-free survival (PFS), overall survival (OS), time to next treatment (TNT), efficacy according to chromosomal translocation-associated gene expression (*CCND1*, *FGFR3*, *MAF* mRNA), proportion of treatment completion and safety. The definitions of the end-points are shown in Supplementary Data S1. Times to first and best responses were also evaluated as *ad hoc* analysis.

We estimated that 41 eligible patients per arm would be required to achieve an 85% probability for observing a 10% higher CR rate in one arm as compared to the other arm, whose CR rate is 20%, based on the Simon's selection design.[14]

Estimating that up to 10% of patients would be ineligible, the sample size was set at 45 in each arm (total 90 patients).

The PFS, OS, and TNT analyses were conducted by the Kaplan–Meier method,[15] and the Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

An interim analysis was conducted whether ORR for each arm was more than the predefined threshold (35%) when 20 patients had been enrolled in each arm. The trhreshold value was based on the MP regimen.[1]

All statistical analyses were performed using SAS software, release 9·4 (SAS Institute, Cary, NC, USA).

Results

Patients

Between July 2013 and April 2016, 91 patients were randomised to Arm A (45 patients) and Arm B (46 patients) from 41 institutions of JCOG-LSG. Patient characteristics (Table I) were well balanced between the arms except for the high-risk group defined by G-banded karyotype and chromosomal translocation-associated gene expression. The median (range) ages of the patients in Arms A and B were 72 (65–79) and 72 (65–78) years, respectively. Thus, no patients aged younger than 65 years were enrolled. The number of patients showing high-risk features characterised by the ectopic expression of *FGFR3* or *MAF* mRNAs were 10 and 1 in Arms A and B, respectively. Abnormal G-banded karyotype was observed in 12 (27%) and 8 (17%) patients in Arms A and B, respectively. All patients received SC bortezomib except for one patient in Arm B who received IV bortezomib. The study profile at the data cut-off date of July 3, 2017 is shown in Fig 2.

Table I. Patient characteristics (n = 91).

	Arm A (n = 45) n (%)	Arm B (n = 46) n (%)
Age, years		
Median (range)	72 (65–79)	72 (65–78)
Gender		
Male/Female	24/21	29/17
ECOG PS		
0/1/2	19/16/4	20/16/2
3 (bone lesions)	6	8
ISS stage		
I–II	36 (80)	39 (85)
III	9 (20)	7 (15)
M-protein class		
IgG	28 (62)	29 (63)
IgA	11 (24)	11 (24)
IgD	0 (0)	1 (2)
Light chains only	6 (13)	5 (11)
End organ damage*		
Hypercalcaemia	6	7
Renal insufficiency	1	3
Anaemia	23	24
Bone lesion	38	39
Hyperviscosity	2	0
G-banded karyotype		
Normal	32 (71)	38 (83)
Abnormal	12 (27)	8 (17)
Not assessed	1 (2)	0 (0)
Chromosomal translocation-associated gene expression (qRT-PCR)		
CCND1	12	18
FGFR3	8	1
MAF	2	0
Not expressed	12	12
Not assessed	12	15

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ISS, International Scoring System; qRT-PCR, quantitative real-time polymerase chain reaction.
*Multiple selects allowed.

Treatment

Median number of treatment cycles was nine (range: 1–9) in Arm A and nine (range: 3–9) in Arm B. The treatment was

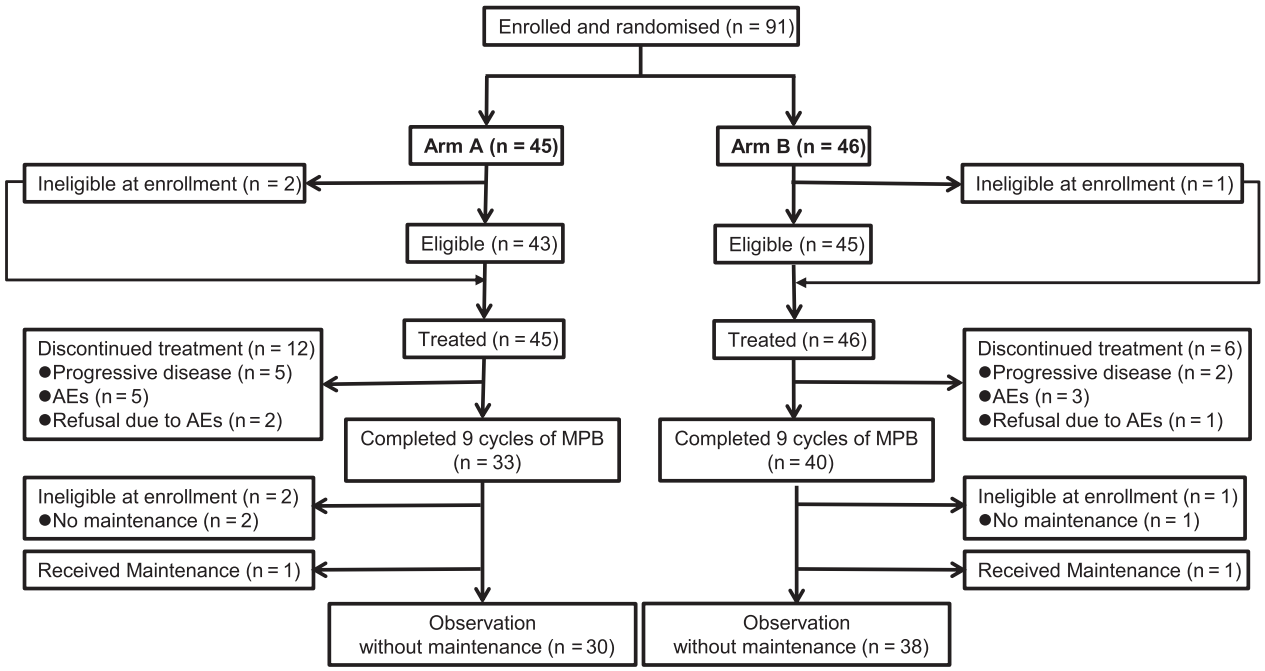

Figure 2. CONSORT Diagram. Flow diagram of randomisation procedure of patients with newly diagnosed multiple myeloma enrolled in the JCOG1105 study comparing two less intensive modified melphalan, prednisolone, and bortezomib (Arms A and B) regimens for selecting a more optimal regimen. PFS, progression-free survival; CI, confidence interval; TNT, time to next treatment; HR, hazard ratio.

Table II. Percentage planned and cumulative doses of melphalan, prednisolone, and bortezomib (n = 91).

	Arm A (n = 45)	Arm B (n = 46)
Total duration of treatment, weeks	46	36
Bortezomib		
Planned dose, mg/m^2	52	35·1
Planned dose intensity, mg/m^2/week	1·13	0·98
Median percentage planned dose, %	88	100
Median cumulative dose, mg/m^2	45·8	35·1
Melphalan		
Planned dose, mg/m^2	324	252
Planned dose intensity, mg/m^2/week	7·04	7·00
Median percentage planned dose, %	100%	100
Median cumulative dose, mg/m^2	324	252
Prednisolone		
Planned dose, mg/m^2	2160	2160
Planned dose intensity, mg/m^2/week	46·96	60
Median percentage planned dose, %	100	100
Median cumulative dose, mg/m^2	2,160	2,160
Median number of treatment cycles	9	9
Percentage treatment completion for all patients (n = 91)	73·3%	87·0%
	95% CI [58·1–85.4]	95% CI [73·7–95.1]
Percentage treatment completion for patients aged 75 years or older (n = 24)	72·7%	76·9%
	95% CI [39·0–94.0]	95% CI [46·2–95.0]

completed in 73·3% (95% CI, 58·1–85·4) of patients in Arm A and 87·0% (95% CI, 73·7–95·1) of patients in Arm B. For patients aged 75 years or older (n = 24), treatment completion proportions were 72·7% (95% CI, 39·0–94·0) in Arm A and 76·9% (95% CI, 46·2–95·0) in Arm B.

Table II shows the percentage planned and cumulative doses of MPB treatment. The planned total doses of bortezomib were 52·0 mg/m^2 in Arm A and 35·1 mg/m^2 in Arm B. Median percentage planned and cumulative doses of bortezomib were 88% and 45·8 mg/m^2 in Arm A, and 100%

and 35·1 mg/m^2 in Arm B. As for melphalan and prednisolone, median percentage planned doses were 100% in both arms.

Responses

At the interim analysis, the ORRs were better than threshold (35%) in both arms, therefore, patient enrolment was continued. Efficacy analyses were performed for all 88 eligible patients. The best responses are shown in Table III. The CR rate (primary end-point) of this randomised phase II study in Arms A and B was 18·6% (95% CI, 8·4–33·4) and 6·7% (95% CI, 1·4–18·3), respectively. The ORR was 79·1% (95% CI, 64·0–90·0) in Arm A and 73·3% (95% CI, 58·1–85·4) in Arm B. The CR rates in predefined subgroups in Arms A and B, respectively, were as follows: age <75 years (15·6% and 3·1%), ≥75 years (27·3% and 15·4%), performance status (PS) 0–1 (15·2% and 8·6%), PS 2–3 (30·0% and 0%), ISS I/II (20·6% and 7·9%), ISS III (11·1% and 0%), no expression of *FGFR3* and *MAF* mRNA (21·7% and 6·7%), and expression of *FGFR3* or *MAF* mRNA (25·0% and 0%).

The median time to first response in Arm A (6·2 weeks) was relatively earlier than that in Arm B (8·1 weeks). Most first responses, including 31 of 34 responders (91·2%) in Arm A and 29 of 33 responders (87·9%) in Arm B, occurred within the first four cycles. Median time to best responses was after the first three cycles in both arms, 16·3 weeks in Arm A and 12·1 weeks in Arm B. Most CRs were confirmed after the first five cycles, six of eight CRs (75%) in Arm A and three of three CRs (100%) in Arm B (Figure S2).

Survivals and time to next treatment

The median follow-up duration was 26 months in all eligible patients. The two-year and median PFSs were 58·1% (95% CI, 41·1–71·7) and 2·5 years in Arm A, and 31·7% (17·8–46·6) and 1·4 years in Arm B, respectively, with a HR (Arm B to Arm A) of 1·93 (95% CI, 1·09–3·42) (Fig 3A). For the intention-to-treat population, the result was much the same: HR is 2·00 (95% CI, 1·13–3·54). The same tendencies were seen in several predefined subgroups including sex, age, PS, ISS, expression of *CCND1*, and expression of *FGFR3* or *MAF* (Figure S3). Median TNTs were 2·7 years in Arm A and 1·5 years in Arm B, respectively, with a HR (Arm B to Arm A) of 1·89 (95% CI, 1·06–3·36) (Fig 3B). The TNTs in predefined subgroups are shown in Figure S4. The two-year OS was 90·2% (95% CI, 75·9–96·2) in Arm A and 92·2% (95% CI, 77·4–97·5) in Arm B (Fig 3C).

Safety

Toxicities observed during treatment are shown in Table IV. The most frequently reported AEs of grade 3 or greater in Arms A and B, respectively, were haematologic, including leukocytopenia (73·3% and 30·4%), neutropenia (64·4% and 28·3%), and thrombocytopenia (35·6% and 10·9%). Sensory peripheral neuropathy of grade 2/3/4 was observed in 24·4/2·2/0% in Arm A and 8·7/0/0% in Arm B. All grades of diarrhoea, nausea, fatigue, fever, and rash occurred more frequently in Arm A, whereas all grades of pneumonitis, herpes zoster, and other infections were more frequent in Arm B.

Table III. Overall and best responses (n = 88)*.

	Arm A (n = 43) n (%)	Arm B (n = 45) n (%)
Overall response†	34 (79·1)	33 (73·3)
Best response		
Stringent complete response	5 (11·6)	2 (4·4)
Complete response	3 (7·0)	1 (2·2)
Very good partial response	10 (23·3)	10 (22·2)
Partial response	16 (37·2)	20 (44·4)
Stable disease	2 (4·7)	10 (22·2)
Progressive disease	2 (4·7)	1 (2·2)
Not evaluable	5 (11·6)	1 (2·2)

*Efficacy analyses were performed for all 88 eligible patients (43 patients in Arm A and 45 patients in Arm B).
†Very good partial response or better.

As shown in Fig 2, discontinuation due to AEs or patient refusal due to AEs were slightly more frequent in Arm A than in Arm B (7 vs. 4 patients). Early termination of treatment within the first four cycles was also more frequent in Arm A (five patients) than in Arm B (one patient); the reasons of early treatment termination of three patients in Arm A were treatment-related AEs including rash, rash with pyrexia, and acute renal failure (one patient each).

Ten patients (six in Arm A and four in Arm B) died during the follow-up period. There was no death during treatment or within 30 days of the last treatment administration. Only one treatment-related death occurred in Arm B due to pneumonitis (suspected cause was *Pneumocystis jirovecii* pneumonia), 103 days after completion of nine cycles of MPB treatment.

Discussion

We compared two different less intensive modified MPB regimens for selecting a more optimal regimen in transplant-ineligible patients with NDMM. We found that Arm A (known as PETHEMA/GEM05 MPB) had a higher CR rate, and better PFS and TNT with more frequent but manageable toxicities as compared to Arm B (further less intensive MPB). The planned total duration of treatment of the two arms differed, i.e. 46 weeks in Arm A and 36 weeks in Arm B. However the median PFS and TNT in Arm A were obviously longer than those in Arm B (2·5 years vs. 1·4 years, and 2·7 years vs. 1·5 years, respectively). This study was not designed to compare OS between arms; the two-year OSs were similar in both arms. In our study, the planned total dose of melphalan in Arms A and B was also different with 324 mg/

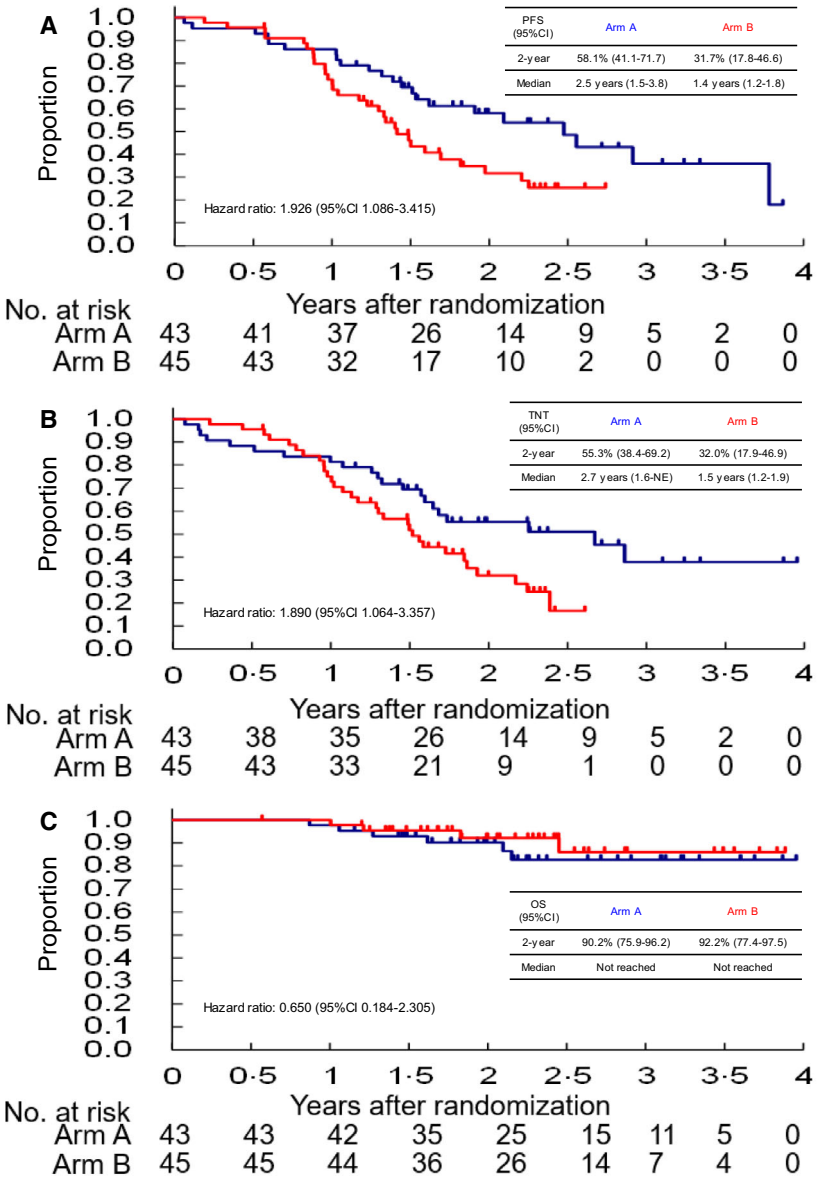

Figure 3. Survivals and time to next treatment. (**A**) Progression-free survival. The two-year and median progression-free survivals were 58·1% (95% CI, 41·1–71·7) and 2·5 years in Arm A, and 31·7% (17·8–46·6) and 1·4 years in Arm B, respectively, with a hazard ratio (Arm B to Arm A) of 1·93 (95% CI, 1·09–3·42). (**B**) Time to next treatment. The two-year and median time to next treatment were 55·3% (95% CI, 38·4–69·2) and 2·7 years in Arm A, and 32·0% (17·9–46·9) and 1·5 years in Arm B, respectively, with a hazard ratio (Arm B to Arm A) of 1·89 (95% CI, 1·06–3·36). (**C**) Overall survival. The two-year overall survival was 90·2% (95% CI, 75·9–96·2) in Arm A and 92·2% (95% CI, 77·4–97·5) in Arm B.

m^2 and 252 mg/m^2, respectively; however, the planned dose intensity was similar for both arms, 7·04 mg/m^2/week in Arm A and 7·00 mg/m^2/week in Arm B (Table II). One explanation for the higher efficacy in Arm A than Arm B might be associated with the higher cumulative dose of melphalan. These results suggested that the twice weekly dosing of bortezomib in the first cycle along with a higher dose of melphalan and a higher cumulative dose of both bortezomib and melphalan influences the efficacy of the modified MPB regimen. To our knowledge, our study is the first randomised trial comparing two different modified MPB regimens.

Previously, the possibility of importance of the cumulative dose of bortezomib on its efficacy was only reported as a *post hoc* analysis of the VISTA study.[6] It was found that the patients who received a higher (≥39 mg/m^2) cumulative dose of bortezomib had a better OS. Although their findings provided clinically important evidence, there were several limitations including the nature of the *ad hoc* analysis. The patients who received a cumulative bortezomib dose <39 mg/m^2 manifested a higher incidence of disease progression or unacceptable toxicities.[16] The median cumulative doses of bortezomib and median PFS after nine cycles of MPB therapy in previous studies were 38·5 mg/m^2 and 22 months (VISTA),[1] 39·4 mg/m^2 and 22 months (GIMEMA MM-03-05),[5] and 42·2 mg/m^2 and 18 months (ALCYONE),[17] respectively. Herein, the median cumulative doses of bortezomib and median PFS were 45·8 mg/m^2 and 30 months in Arm A, and 35·1 mg/m^2 and 17 months in Arm B, respectively. The relatively longer PFS in Arm A could be associated with the higher cumulative dose of bortezomib.

The dosing schedules of bortezomib in the MPB regimens in the previous studies, including VISTA,[1] PETHEMA/GEM05,[3]

Table IV. Adverse events (n = 91).

	Arm A (n = 45)						Arm B (n = 46)					
NCI-CTCAE v4·0	G1	G2	G3	G4	Total%	G3/4%	G1	G2	G3	G4	Total%	G3/4%
Leukopenia	1	11	31	2	100	73·3	5	17	13	1	78·3	30·4
Neutropenia	2	13	20	9	97·8	64·4	11	16	8	5	87	28·3
Anaemia	6	22	16	1	100	37·8	11	24	11	0	100	23·9
Thrombocytopenia	20	9	11	5	100	35·6	26	10	5	0	89·1	10·9
Hyponatraemia	32	–	8	0	88·9	17·8	34	–	8	0	91·3	17·4
ALT increased	28	4	5	1	84·4	13·3	18	3	4	1	56·5	10·9
PN: sensory	18	11	1	0	66·7	2·2	9	4	0	0	28·3	0
PN: motor	2	4	0	0	13·3	0	3	2	1	0	13	2·2
Constipation	17	10	0	0	60	0	12	12	0	0	52·2	0
Diarrhoea	10	5	4	0	42·2	8·9	5	3	1	0	19·6	2·2
Nausea	7	9	1	–	37·8	2·2	6	4	1	–	23·9	2·2
Anorexia	13	8	2	0	51·1	4·4	7	7	2	0	34·8	4·3
Fatigue	19	8	–	–	60	–	11	6	–	–	37	–
Fever	13	5	2	0	44·4	4·4	17	2	0	0	41·3	0
Any skin disorders	7	9	3	0	42·2	6·7	8	6	2	0	34·8	4·3
Pneumonitis	0	1	0	0	2·2	0	0	2	2	0	8·7	4·3
Herpes zoster	–	1	0	0	2·2	0	–	2	0	0	4·3	0
Any infections	1	12	2	0	33·3	4·4	0	11	5	0	34·8	10·9

NCI-CTCAE v4.0, National Cancer Institute-the Common Terminology Criteria for Adverse Events version 4.0.; G, grade; ALT, alanine aminotransferase; PN, peripheral neuropathy.

and GIMEMA MM-03-05,[5] were different. None of the randomised studies directly compared original twice weekly dosing with modified once weekly bortezomib dosing in MPB regimens. A less intensive dosing schedule with limited[3] or no twice weekly[5] bortezomib administration as induction therapy could achieve a similar cumulative dose of bortezomib and outcomes with reduced toxicities.[4,18,19] Presently, the modified MPB regimen is considered a standard induction regimen in patients with transplant-ineligible NDMM; however, the impact of initial twice weekly bortezomib dosing on efficacy of the modified MPB regimen has remained unclear. We showed that the median time to first response in Arm A (6·2 weeks; i.e. after the first cycle) occurred relatively earlier than that in Arm B (8·1 weeks; i.e. after the second cycle). The twice weekly bortezomib dosing in the first cycle of MPB in Arm A resulted in rapid initial response, which may benefit patients with NDMM, especially those with clinically symptomatic and aggressive disease. In patients with PS 2–3 at study enrolment, the PFS in Arm A tended to show better than that in Arm B (median 2·5 vs. 1·2 years, respectively) (Figure S3). As our eligibility criteria permitted the enrolment of patients with PS 3 only resulting from osteolytic lesions, rapid responses to treatment and improvement of patients' condition could have resulted in better PFS in Arm A.

The CR rate in our study (18·6% in Arm A and 6·7% in Arm B) was relatively lower than that in the VISTA (33%)[1] and other modified MPB studies (PETHEMA/GEM05: 20%,[3] GIMEMA MM-03-05: 23%,[5] and ALCYONE: 24·4%).[17] One possible reason was failure to confirm CR through a second response assessment in some patients, because all response categories require two consecutive assessments according to the IMWG response criteria.[8]

Haematologic toxicities, sensory peripheral neuropathy, gastrointestinal toxicities, fatigue, fever and rash were more frequent in Arm A, as expected. As for haematologic toxicities, incidence of any grade was similar in both arms; however, higher grade toxicity in Arm A we more than double that observed in Arm B. Additionally, sensory peripheral neuropathy of any grade in Arm A was more than double that observed in Arm B, while grade 3 or higher was observed in 2·2% of patients in Arm A, and no patients in Arm B; this was lower than that of the Japanese phase I/II study of MPB (10%)[2] and the VISTA trial (13%).[1] Furthermore, the rate of fatigue was 60% in Arm A and 37% in Arm B, even though all grades were either 1 or 2.

To date, a threshold of bortezomib dose reduction with preserved efficacy in the MPB regimen remains unclear. As for Arm B, consisting of nine cycles of bortezomib given in three weekly doses plus melphalan and prednisolone on days 1–4 of a four-week cycle, we expected that the further less intensive and better tolerated MPB regimen could reduce early treatment discontinuations, bortezomib dose reduction, and shows better outcomes with a convenient four-week schedule and shorter treatment duration (total 36 weeks). As a result, the proportion of treatment completion in Arm B was relatively higher (87%) than that in Arm A (73·3%) and in previous MPB studies (37·4% in VISTA,[1] 69·2% in PETHEMA/GEM05,[3] and 65·3% in GIMEMA-MM03-05[5]), and the median percentage planned doses of bortezomib in Arm B was 100%. However, CR rate in Arm B was lower

(6·7%) than that in Arm A (18·6%), and both PFS and TNT were shorter. One explanation is that the planned dose of bortezomib in Arm B (35·1 mg/m^2) was too low to obtain a sufficient efficacy. However, there is a significant heterogeneity among patients, and since the toxicity profile in Arm B was considerably better than that in Arm A and that OS did not differ, the Arm B regimen (once weekly bortezomib and dose reduction of melphalan) may be one treatment option for certain patients, particularly those who are frail, especially in clinical practice.

A prospective randomised trial is an effective way to evaluate the impact of cumulative bortezomib dose (in MPB therapy) on outcomes in patients with NDMM. Recently, use of anti-CD38 monoclonal antibody, daratumumab, in combination with MPB has shown significant clinical benefits as compared with MPB in the phase III ALCYONE study.[17,20] Our (JCOG1105) data will support the usefulness of ALCYONE's MPB because the MPB regimen adopted in ALCYONE study was similar to Arm A of JCOG1105. Currently, several treatment regimens in combination with lenalidomide–dexamethasone (Ld), such as bortezomib–Ld[21] and modified version,[22] daratumumab–Ld,[23,24] elotuzumab–Ld,[25] and carfilzomib–Ld[26] have been developed. However, there is no randomised trial comparing MPB-based regimens with other regimens, therefore MPB-based regimens, such as daratumumab–MPB, would continue to be one of the standard induction regimens for patients with transplant-ineligible NDMM, especially in high-risk patients.[27]

In conclusion, our results propose that the twice weekly dosing of bortezomib in the first cycle along with a higher dose of melphalan and a higher cumulative dose of both bortezomib and melphalan influences the efficacy of the modified MPB regimen as an induction treatment in patients with transplant-ineligible NDMM. Based on the results of this (JCOG1105) study, we are planning for a next clinical trial incorporating a novel agent and assessment of high-risk cytogenetics and minimal residual disease.

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Author contributions

DM, SI and GO conceived and designed the study; all authors provided study materials and recruited patients; DM, SI and GO collected, analysed, and interpreted the data; DM, SI and GO wrote the manuscript; all authors gave final approval of the manuscript.

Conflicts of interest

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplemental data of JCOG1105

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