

LETTER TO THE EDITOR

Final analysis of randomized phase II study optimizing melphalan, prednisolone, bortezomib in multiple myeloma (JCOG1105)

We conducted a randomized phase II study to determine a more promising modified MPB regimen for TI-NDMM (JCOG1105, jRCTs031180097). The primary analysis in JCOG1105 revealed that Arm A (known as PETHEMA/GEM05 MPB) showed a higher CR rate and longer PFS without intolerable toxicities compared with Arm B (a further less intensive MPB) at a median follow-up period of 26 months, suggesting that the twice-weekly dosing of bortezomib in the first cycle along with a higher dose of melphalan and higher cumulative dose of both bortezomib and melphalan influenced the efficacy of the modified MPB regimen in patients with TI-NDMM¹ (Appendix S1). Here, we report the updated results from preplanned analysis of JCOG1105 with a 3-year follow-up from the end of accrual.

Between July 2013 and April 2016, in total 91 patients were randomized to Arm A (45 patients) and Arm B (46 patients). As for the data cut-off (June, 2019), the median follow-up period of all eligible patients was 47.3 months (range 10.4–71.1). The PFS rates at 1, 3, and 5-years (95% CI) were 86.0% (71.6%–93.5%), 27.9% (15.6%–41.6%), and 16.4% (5.8%–31.8%) in Arm A, and

73.3% (57.8%–83.9%), 13.3% (5.4%–24.9%) and not estimable in Arm B with the HR of Arm B to Arm A being 1.69 (95% CI 1.06–2.68; Figure 1A). Predefined subgroup analyses of PFS are shown in Figure 2. Female patients seemed to have better PFS in Arm A (HR in Arms B to A, 2.87 [95% CI 1.34–6.61]) compared with male patients (HR in Arms B to A, 1.18 [95% CI 0.66–2.13]; Figure 2A,B), and patients with PS 2-3 also showed a tendency to have better PFS in Arm A (HR in Arms B to A, 4.32 [95% CI 1.42–13.1]), unlike patients with PS 0-1 (HR in Arms B to A, 1.44 [95% CI 0.85–2.45]; Figure 2C,D). The OS rate at 5 years was 73.4% (95% CI 54.8%–85.3%) in Arm A and 56.8% (95% CI 31.2%–76.0%) in Arm B, respectively (HR in Arms B to A, 1.58 [95% CI 0.71–3.53]) (Figure 1B). The OS was similar between Arms A and B. In total, 25 patients (10 in Arm A and 15 in Arm B) died during the follow-up period, with a tendency toward numerical imbalance regarding death from myeloma (six in Arm A and 11 in Arm B). In comparison with AEs reported in the primary analysis,¹ there were no marked changes in the incidence and severity of AEs reported in the final analysis.

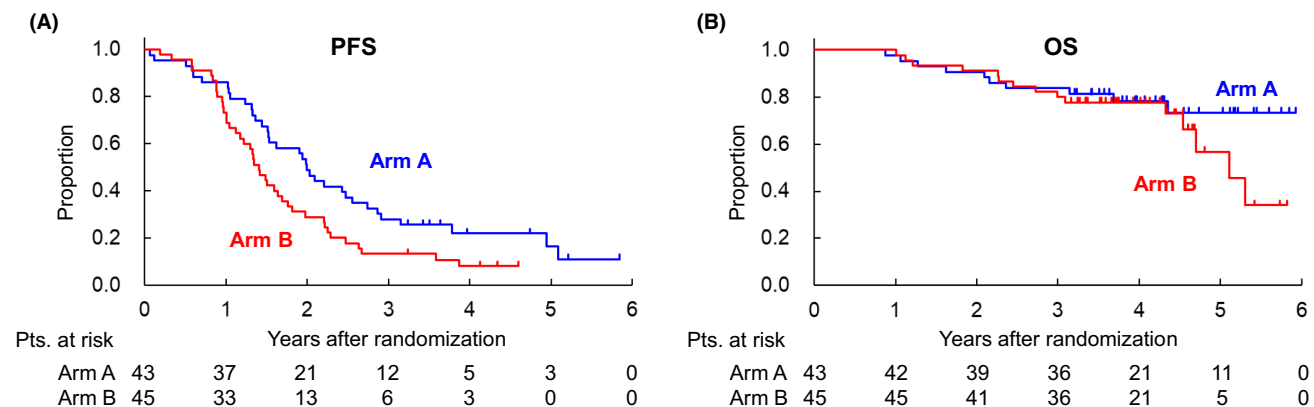


FIGURE 1 PFS and OS. (A) The 5-year PFS was 16.4% (5.8%–31.8%) in Arm A, and not estimable in Arm B. (B) The 5-year OS was 73.4% (95% CI 54.8%–85.3%) in Arm A and 56.8% (95% CI 31.2%–76.0%) in Arm B

Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; HR, hazard ratio; JCOG, Japan Clinical Oncology Group; MPB, melphalan, prednisolone, bortezomib; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PS, performance status; TI-NDMM, transplant-ineligible newly diagnosed multiple myeloma.

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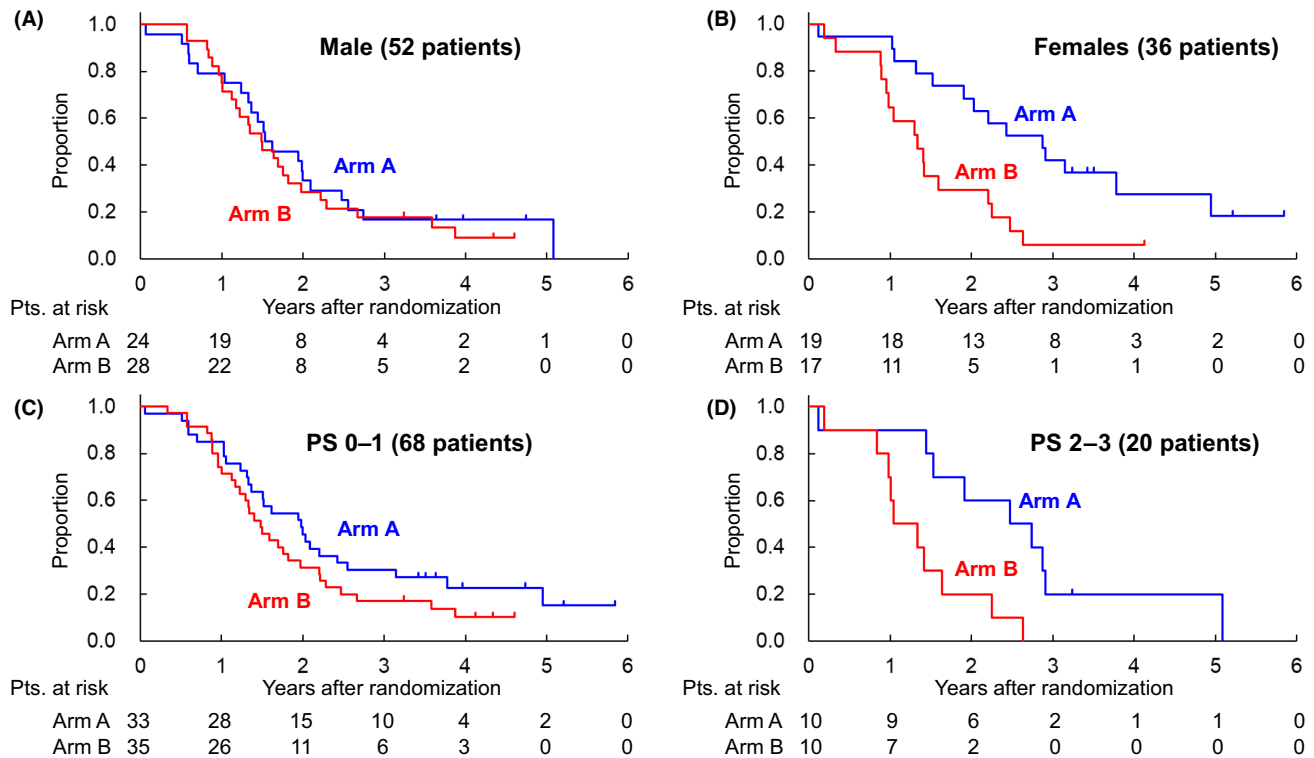


FIGURE 2 PFS of predefined subgroups. (A, B) Female patients seemed to have better PFS in Arm A unlike male patients. (C, D) PS 2-3 seemed to have better PFS in Arm A unlike PS 0-1

TABLE 1 Second primary malignancies

Arm	Second primary malignancy	Onset of second primary malignancy after protocol treatment	Subsequent treatment
Arm A	Early gastric cancer	214 days	None
Arm B	Esophageal cancer	31 months	Lenalidomide/dexamethasone
	Acute myeloid leukemia	26 months	Lenalidomide/dexamethasone
	Cutaneous squamous cell carcinoma	106 days	None
	Prostate cancer	23 months	Lenalidomide/dexamethasone
	Intramucosal gastric cancer	35 months	Lenalidomide/dexamethasone

There are no reports regarding the influence of gender on the survival of patients with T1-NDMM who were treated with a bortezomib-containing regimen, and the reason why female patients seemed to have a better PFS in Arm A in the present study seemed to be unclear. Although there was a slight imbalance in the number of patients with International Staging System (ISS) stage III (14 males and two females) and expression of adverse chromosomal translocation-associated genes (FGFR3 or MAF mRNA; three males and seven females), other patient characteristics, treatment exposure including percentage planned dose of bortezomib, melphalan, and prednisolone and incidence of AEs were similar between female and male patients. Among patients with PS 2-3 at study enrollment (10 patients each in both arms), the long-term PFS in Arm A also tended to be better compared with that in Arm B. As our eligibility criteria permitted the enrollment of patients with PS 3 only resulting from osteolytic lesions (six patients in Arm A and eight patients in

Arm B), rapid responses to treatment and improvement of patients' condition could have resulted in better PFS in Arm A.

In JCOG1105, although a higher median cumulative dose of melphalan was administered in Arm A (324 mg/m²) compared with in Arm B (252 mg/m²), a lower incidence of second primary malignancies was observed in Arm A (one patient) compared with in Arm B (five patients; Table 1). This result was consistent with the long-term follow-up findings of the VISTA study² that showed no increased risk of second primary malignancies with MPB.

In summary, the final analysis of JCOG1105 demonstrated that twice-weekly dosing of bortezomib in the first cycle along with higher dose of melphalan and higher cumulative dose of both bortezomib and melphalan (Arm A) confers sustained PFS benefit with no new AE-related concerns. However, a continued risk of relapse was observed in both arms because maintenance therapy was not recommended and all patients except two did not receive maintenance

therapy in JCOG1105. Based on the results of this study, we are now conducting a next clinical trial incorporating anti-CD38 antibody and fixed-duration maintenance therapy combined with a modified MPB regimen and assessment of high-risk cytogenetics and MRD (JCOG1911; jRCTs031200320).

AUTHOR CONTRIBUTION

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

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DISCLOSURE

DM reports honoraria (Janssen, Mundipharma, Eisai, Chugai); research funding (Celgene, Novartis, Chugai, Ono, Takeda, Janssen, MSD). SI, an editorial board member of Cancer Science, reports honoraria (Celgene, Sanofi, Janssen, Takeda, Ono, Bristol Myers Squibb); research funding (Bristol Myers Squibb, Celgene, Janssen, Daiichi Sankyo, Amgen, Ono, AbbVie, GlaxoSmithKline, Eli Lilly, Caelum, Pfizer, Takeda, Sanofi). RM has nothing to disclose. SK reports honoraria (Chugai, Kyowa Kirin, Janssen, Daiichi Sankyo); research funding (Chugai, Kyowa Kirin, Janssen, Daiichi Sankyo). NF reports honoraria (Chugai, Kyowa Kirin, Huya Japan); research funding (AbbVie, Bayer, Chugai, Celgene, Eisai, Gilead, Incyte, Ono, Solasia). NY, KM, and MY have nothing to disclose. JK reports honoraria (Janssen). NT and HT have nothing to disclose. KU reports honoraria (Novartis Pharma); research funding (Astellas Pharma, AbbVie, Apellis, Symbio, Daiichi Sankyo, Novartis, Janssen, Otsuka, Astellas-Amgen-Biopharma, Takeda, Nippon Shinyaku, Bristol Myers Squibb). TY reports honoraria (Janssen). TU and IM have nothing to disclose. YT reports honoraria (Takeda, Janssen, Celgene); scholarship (Chugai, Takeda, Taiho, Astellas, Ono). YN has nothing to disclose. SO reports honoraria (Novartis, Bristol Myers Squibb); research funding (Kyowa Kirin). EO has nothing to disclose. IH reports honoraria (Bristol Myers Squibb, Takeda, Celgene, Sanofi, Janssen); research funding (Bristol Myers Squibb, Celgene). YS, SY, SY, YS, YK, and SF have nothing to disclose. KT reports honoraria (Daiichi Sankyo, Chugai, Byer, Kyowa Kirin, HUYA BIO, Bristol Myers Squibb). HN reports honoraria (Celgene, Esai, Chugai, Ono, Mundipharma); research funding (Bayer, AstraZeneca,

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ETHICS STATEMENT

Approval of the research protocol: The study protocol was approved by the Protocol Review Committee of JCOG, and was reviewed and approved by the National Cancer Center Hospital Certified Review Board (CRB3180008).

Informed consent: Written informed consent was obtained from all the patients.

Registry and registration No. of the trial: jRCTs031180097.

Animal studies: N/A.

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REFERENCES

1. Maruyama D, Iida S, Ogawa G, et al. Randomised phase II study to optimise melphalan, prednisolone, and bortezomib in untreated multiple myeloma (JCOG1105). *Br J Haematol*. 2021;192(3):531-541.
2. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010;28(13):2259-2266.

SUPPORTING INFORMATION

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