

## Alternating bortezomib-dexamethasone and lenalidomide-dexamethasone in patients with newly diagnosed multiple myeloma aged over 75 years

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### ABSTRACT

More than 40% of Japanese patients with multiple myeloma (MM) are over 75 years of age at diagnosis. Regardless of the treatment benefits, complications and relapses obstruct long-term survival. We conducted a phase II, open-label, single-arm, multicenter clinical trial to assess the efficacy and safety of alternating bortezomib-dexamethasone (Bd) and lenalidomide-dexamethasone (Ld) (Bd/Ld) treatment in MM patients aged over 75 years (MARBLE trial). Patients received Bd therapy from days 1 to 35 and Ld therapy from days 36 to 63. For Bd therapy, patients were administered bortezomib 1.3 mg/m<sup>2</sup> and oral dexamethasone 20 mg on days 1, 8, 15, and 22. For Ld therapy, they were administered lenalidomide 15 mg from days 36 to 56 and dexamethasone 10 mg on days 36, 43, 50, and 57. They underwent six treatment cycles in total, each consisting of a 63-day regimen. In total, 10 patients were enrolled, with a median age of 81 years. Efficacy was not evaluated because the patients were fewer than planned. The overall response rate was 80.0% and complete response rate 40.0%. Seventy percent of patients completed the study treatment. Progression-free survival and overall survival at 2 years were 40.0% and 80.0%, respectively. Adverse events of grade 3 or higher, including anemia, decreased lymphocyte count, neutropenia, and hypokalemia, were observed in eight patients. Alternating chemotherapy with Bd/Ld might be feasible, but its efficacy should be verified further.

Keywords: myeloma, alternating therapy, bortezomib, lenalidomide, dexamethasone

Received: November 25, 2020; accepted: May 21, 2021

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Abbreviations:

AEs: adverse events  
ASCT: autologous stem cell transplantation  
BMP: bortezomib/melphalan/prednisone  
Bd: bortezomib-dexamethasone  
Bd/Ld: bortezomib-dexamethasone and lenalidomide-dexamethasone  
CI: confidence interval  
CRR: complete response rate  
FIRST trial: Frontline Investigation of Revlimid and Dexamethasone Versus Standard Thalidomide trial  
Ld: lenalidomide plus low-dose dexamethasone  
MM: multiple myeloma  
NDMM: newly diagnosed multiple myeloma  
ORR: overall response rate  
OS: overall survival  
PFS: progression-free survival  
TTR: time to response  
UMIN: University Hospital Medical Information Network  
VGPR: very good partial response  
VISTA trial: Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone trial

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## INTRODUCTION

Multiple myeloma (MM) is caused by an accumulation of cancerous plasma cells, the terminally differentiated form of B-lymphocytes, in the bone marrow, and it is characterized by the production of an abnormal protein called monoclonal immunoglobulin (M-protein) by the tumor cells. This refractory disease shows several clinical symptoms, including hypercalcemia, renal insufficiency, anemia, and bone osteolytic changes, otherwise known as CRAB criteria, even in the novel agent era.<sup>1</sup>

Nevertheless, radical improvements in treatment outcomes have been accomplished by treatment with high-dose melphalan plus autologous stem cell transplantation (ASCT) as well as with novel chemotherapeutic agents, including bortezomib, lenalidomide, and thalidomide. However, these treatments have failed to improve long-term survival in elderly patients, who are generally ineligible for ASCT. Therefore, the greatest therapeutic benefits of these treatments are limited to patients under 70 years of age, mainly due to adverse events (AEs).<sup>2</sup>

Based on data from randomized phase III trials, the following two treatment options are recommended for elderly patients: bortezomib/melphalan/prednisone (BMP), based on the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) trial<sup>3</sup> and lenalidomide plus low-dose dexamethasone (Ld), based on the Frontline Investigation of Revlimid and Dexamethasone Versus Standard Thalidomide (FIRST) trial.<sup>4</sup> In Japan, both BMP and Ld are approved as front-line options.

Further, combination therapy with bortezomib-dexamethasone (Bd) has been investigated, mainly by the UPFRONT trial, a community-based phase IIIB study in the US, performed to compare three front-line regimens based on bortezomib (Bd, BMP, and Bd plus thalidomide) in ASCT-ineligible patients with MM; the study results suggested that a Bd treatment regimen balances efficacy and safety in elderly MM patients.<sup>5</sup>

To further improve the treatment outcome in this population, a triplet combination of bort-

ezomib plus Ld administered in a modified dose and schedule was examined; it was found to be a well-tolerated and effective treatment option for newly diagnosed MM (NDMM) patients aged over 65 years.<sup>6</sup>

Presently, despite the known benefits of these novel agents, most patients pass away after repeated relapses. There is little evidence supporting alternating chemotherapy as a treatment strategy for MM. The international phase II trial by Mateos MV et al comparing BMP and Ld administered in a sequential (121 patients) and alternating (120 patients) manner did not show differences in efficacy and safety between the two groups.<sup>7</sup> In this study, Ld was administered after the start of bortezomib treatment because Ld was not approved for newly diagnosed or untreated MM in Japan when this study was designed. In our study, we investigated an alternating chemotherapy regimen of Bd and Ld (alkylator-free regimen) with respect to balancing safety, tolerability, and efficacy in elderly patients with ASCT-ineligible NDMM. We assumed that the side effects will be suppressed by alternating two drugs with different mechanisms of action as an initial treatment strategy for MM, leading to high efficacy and improved survival. Furthermore, we detected chromosomal abnormalities in patients using fluorescence in situ hybridization (FISH) and assessed whether the alternating treatment strategy suppresses clonal evolution.

## METHODS

### *Trial design*

In this phase II, open-label, single-arm, multicenter trial, we assessed the efficacy and safety of alternating Bd and Ld as an induction therapy for NDMM patients aged 75 years or more who were ineligible for ASCT. Patients who satisfied the eligibility criteria were enrolled in the study. The details of this study are described elsewhere.<sup>8</sup>

This study was performed at 22 facilities in Japan and was registered in the Clinical Trial Registry of the University Hospital Medical Information Network (UMIN), Japan (Registration Number: UMIN000013773).

### *Interventions*

Patients were enrolled in the trial within 4 weeks of diagnosis and began treatment according to the study protocol. Patients received Bd therapy from days 1 to 35 (for 35 days) and Ld therapy from days 36 to 63 (for 28 days). Patients underwent a total of six treatment cycles, each consisting of a 63-day regimen, as mentioned above. The starting doses of bortezomib and lenalidomide were adjusted based on patient age, general condition, and renal function.

For Bd therapy, patients were administered bortezomib 1.3 mg/m<sup>2</sup> and oral dexamethasone 20 mg on days 1, 8, 15, and 22. The site of bortezomib administration was rotated between sessions to avoid consecutive injections at the same site (eg, left thigh, right thigh, abdomen). Following Bd therapy, patients were administered lenalidomide 15 mg from days 36 to 56 and dexamethasone 10 mg on days 36, 43, 50, and 57 as Ld therapy. A physician decided whether each patient should receive treatment in an inpatient or outpatient setting.

It was recommended to administer antibacterial agents, antifungal agents, or sulfamethoxazole-trimethoprim to prevent infectious diseases and to use anticoagulants or antiplatelet agents to prevent deep vein thrombosis in patients who were concerned about the increase in the risk of venous thromboembolism.

We performed the chromosome test (G-binding) and FISH test at baseline 2–4 weeks before the treatment started. The myeloma FISH panel included the following: Vysis LSI IGH/CCND1 XT Dual Color Dual Fusion Probes probe to detect t(11;14)(q13;q32), Vysis LSI IGH/FGFR3

Dual Color Dual Fusion Probes to detect t(4;14)(p16;q32), Vysis LSI IGH/MAF Dual Color Dual Fusion Probes probe to detect t(14;16)(q32;q23), Vysis LSI IGH/MYC/CEP 8 Tri-Color Dual Fusion FISH Probes to detect t(8;14)(q24;q32), Vysis LSI D13s319/13q34 FISH Probes to detect deletion of 13q14, Vysis LSI TP53 SpectrumOrange/ CEP 17 SpectrumGreen Probes to detect deletion of p53 (17p13.1), CKS1B/CEN1p Dual Color FISH Probe to detect chromosome 1q21 gain, AHCYL1/CEN1p Dual Color FISH Probe to detect deletion of 1p13, and CDKN2C/CEN1p Dual Color FISH Probe to detect deletion of 1p32.

Further, we conducted a comprehensive geriatric assessment, including the Cumulative Illness Rating Scale for Geriatrics, at baseline.<sup>9</sup>

### Sample size

One trial reported that Ld therapy achieved an overall response rate (ORR) of 70.4% in untreated MM patients aged 75 years or older.<sup>10</sup> In contrast, the EVOLUTION study revealed ORRs of 85% and 88% for bortezomib-lenalidomide-dexamethasone and bortezomib-dexamethasone-cyclophosphamide-lenalidomide therapies in a population of untreated MM patients, respectively.<sup>11</sup> We expected our approach of alternating chemotherapy with Bd and Ld to achieve an ORR of 88%. Thereby, the required sample size was calculated as  $n = 32$ , assuming an expected response rate of 88%, a threshold response rate of 70.4%,  $\alpha = 0.05$  (one-sided), and  $\beta = 0.2$  (80% power), based on a binomial distribution. However, we set the sample size at 35 according to a dropout rate of 10%.

### Statistical methods

The primary endpoint was the ORR during the period of alternating chemotherapy with Bd and Ld. Secondary endpoints were AEs, the proportion of treatment continuation, complete response rate (CRR), very good partial response (VGPR), progression-free survival (PFS), overall survival (OS), and time to response (TTR).

ORR, CRR and VGPR were estimated with 90% confidence intervals (CIs). Survival curves of PFS, OS and TTR were calculated using the Kaplan–Meier method; CI was calculated using Greenwood's formula. Further, the occurrence of worst-grade AEs, grade-3 or higher AEs, and serious AEs were calculated.

## RESULTS

### Patient demographics

Ten patients were enrolled between October 2014 and March 2016 from three centers of the National Hospital Organization in Japan. The study ended before reaching the target sample size because of slow accrual. All patients (five men and five women) were included in the intention-to-treat analysis. Patient characteristics are shown in Table 1.

**Table 1** Patient characteristics

	n (%) <sup>*</sup>
Number of patients	10
Gender	
Male	5 (50.0%)
Female	5 (50.0%)

Age (years)	81 (76–85)
Durie & Salmon System stage	
II	2 (20.0%)
III	8 (80.0%)
International Staging System stage	
I	1 (10.0%)
II	5 (50.0%)
III	4 (40.0%)
ECOG Performance Status score	
1	3 (30.0%)
2	3 (30.0%)
3	4 (40.0%)
Serum M protein type	
IgG	4 (40.0%)
IgA	5 (50.0%)
BJP	1 (10.0%)
Bone lesion	
Osteoporosis	3 (30.0%)
Osteolytic lesions	2 (20.0%)
Extensive bone destruction and major fractures	5 (50.0%)
Translocation karyotype/Chromosome abnormality	
t(11;14)(q13;q32), other	1 (10.0%)
Other	1 (10.0%)
Chromosome 13 abnormalities -13/13q-	1 (10.0%)
FISH abnormalities (n = 9)	
t(4;14)(p16;q32)	3 (33.3%)
t(8;14)(q24;q32)	1 (11.1%)
t(11;14)(q13;q32)	2 (22.2%)
del(17p)	1 (11.1%)
del(1p32.3)	1 (11.1%)
1q21 gain	5 (55.6%)
del(13)	5 (55.6%)
Other (n = 3)	1 (33.3%)
Serum $\beta$ 2-microglobulin (mg/L)	5.3 (3.1–9.5)
Albumin (g/dL)	3.2 (2.5–4.0)
Hb (g/dL)	4.4 (3.9–4.9)
Creatinine clearance (mL/min)	45.8 (31.8–66.7)
Ca (mg/dL)	9.5 (7.2–11.3)
LDH (U/L)	167 (121–253)
Ratio of bone marrow plasma cells	41.6 (9.0–80.4)
Comorbidity <sup>#</sup>	
Vascular	6 (60.0%)
Respiratory	2 (20.0%)
Eyes, ears, nose, throat, and larynx	1 (10.0%)

Liver, pancreas, and biliary	1 (10.0%)
Renal	5 (50.0%)
Neurologic	1 (10.0%)
Endocrine and breast	2 (20.0%)
Psychiatric illness	1 (10.0%)

\*Data are presented as median (range) or number (%).

BJP: Bence Jones proteinuria

Ca: calcium

ECOG: Eastern Cooperative Oncology Group

FISH: fluorescence in situ hybridization

Hb: hemoglobin

IgA: immunoglobulin A

IgG: immunoglobulin G

LDH: lactate dehydrogenase

#Scores ≥ 2, assessed with the Cumulative Illness Rating Scale-Geriatric during comprehensive geriatric assessment.

The median age was 81 years (range, 76–85 years). Eight patients (80.0%) had stage III MM according to the Durie and Salmon system. All patients had Eastern Cooperative Oncology Group Performance Status score ≥ 1; three (30.0%) had score 1, three (30.0%) had score 2, and four (40.0%) had score 3. In terms of the serum M protein type, five (50.0%), four (40.0%), and one (10.0%) patients had IgA, IgG, and Bence Jones protein, respectively. In one patient, the translocation karyotype was t(11;14)(q13;q32). FISH abnormalities were observed as follows: five patients with 1q21 gain, five with del(13), three with t(4;14)(p16;q32), two with t(11;14)(q13;q32), one with t(8;14)(q24;q32), one with del(17p), and one with del(1p32.3). Six patients were categorized into the high-risk subgroup with chromosomal abnormalities: t(4;14), t(14;16), del(17p), or 1q21 gain, as determined by the International Myeloma Working Group and Mayo Clinic.<sup>12,13</sup> All patients had bone lesions, and the median serum β2-microglobulin level of 5.3 mg/L (range 3.1–9.5 mg/L) was high. Among out of the 10 patients, 7 (70.0%) completed the trial planned six treatment of 6 cycles.

The remaining three patients discontinued up to six cycles of Bd therapy, during four cycles of Bd therapy, and after three cycles of Bd therapy. The reasons for early treatment discontinuation were extended treatment interval (n = 2) and patient request (n = 1).

*Outcomes*

The maximum effect of patient response is shown in Table 2.

**Table 2** Maximum effect of patient response

	sCR	CR	VGPR	PR	SD	Total (n)	ORR
Bd/Ld	3	1	2	2	2	10	80.0%

Bd: bortezomib-dexamethasone

Ld: lenalidomide-dexamethasone

sCR: stringent complete response

CR: complete response

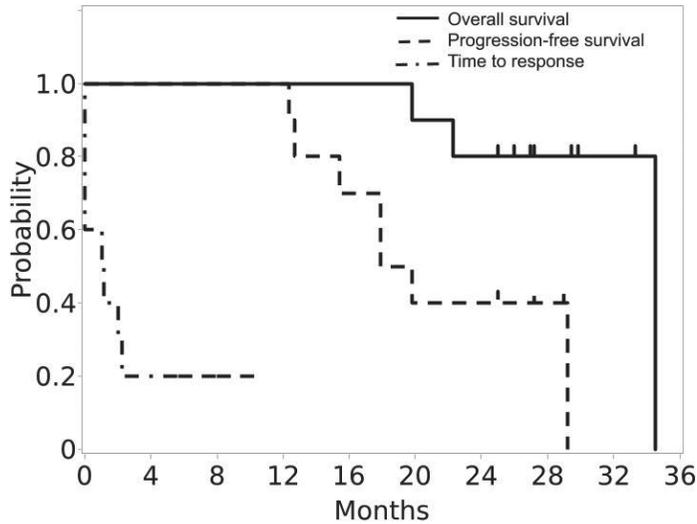
VGPR: very good partial response

PR: partial response

SD: stable disease

The ORR was 80.0% (90% CI: 49.3–96.3%), CRR was 40%, and VGPR rate was 20% for Bd/Ld alternating treatment, with seven patients (70.0%) having completed the planned six cycles of study treatment. In two patients, the effect worsened when the treatment was switched from Ld to Bd.

At the cut-off date (January 15, 2018), the median follow-up time was 27 months. The 2-year OS and PFS were 80.0% and 40.0% (95% CI: 40.9–94.6%, 12.3–67.0%), respectively (Fig. 1).



**Fig. 1** Kaplan-Meier curve for overall survival, progression-free survival, and time to response

Four out of six patients with relapse or disease progression received the first salvage therapy with immunomodulatory drugs (IMiDs). Moreover, two patients additionally received second salvage therapy with IMiDs or bortezomib. Regarding the response time, the probability at 10 months was 20.0% (95% CI: 3.1–47.5%). Three patients from the high-risk subgroup died during the follow-up period due to myeloma.

Of the total 10 patients, 8 had AEs of grade 3 or higher, the most common of which were hematologic toxicities, such as anemia, lymphocyte count decrease, neutropenia, platelet count decrease, and white blood cell decrease, as shown in Table 3. Grade 4 AEs of neutropenia, lymphocyte count decrease, platelet count decrease, and white blood cell decrease were observed in one patient during cycle 4 of Bd therapy.

**Table 3** Adverse events of grade 3 or more

Cycle	1		2		3		4		5		6	
	Bd	Ld										
n	10	10	10	10	10	9	9	8	8	8	7	7

NHOH-MARBLE study

Anemia	3	1	2	1	1	0	1	0	0	0	0	0
Diarrhea	0	0	1	0	0	0	0	0	0	0	0	0
Nausea	0	1	0	0	0	0	0	0	0	0	0	0
Infections, infestations, and others	0	0	0	0	0	0	1	0	0	0	0	0
Lymphocyte count decrease	1	2	0	2	0	0	1	0	0	0	0	1
Neutropenia	2	0	1	1	1	1	1	0	0	0	0	0
Platelet count decrease	1	1	0	0	0	0	1	0	0	0	0	0
White blood cell count decrease	1	1	1	1	1	1	1	0	0	0	0	0
Anorexia	0	0	0	0	0	0	1	0	0	0	0	0
Hypokalemia	0	0	1	2	1	1	0	0	0	0	0	0
Hyponatremia	1	0	0	0	0	0	0	0	0	0	0	0
Back pain	1	0	0	0	0	0	0	0	0	0	0	0
Bone pain	1	0	0	0	0	0	0	0	0	0	0	0

Two patients experienced unexpected serious AEs; one had grade 2 arthralgia and the other grade 3 musculoskeletal and connective tissue disorders. The former was diagnosed as osteoarthritis of the hip; subsequently, bortezomib on day 22 was omitted, and the patient recovered after undergoing joint arthroplasty. The latter was diagnosed as a fracture of the right femoral neck and was resolved with an arthroplasty. We discontinued the study treatment for the latter patient.

In terms of its association with the number of treatment cycles, the number of AEs of grade

3 or higher decreased after cycle 4 of Ld treatment, and only one case of lymphocyte count decrease occurred at cycle 6 of Ld treatment.

## DISCUSSION AND CONCLUSION

In the present study, we evaluated the feasibility and efficacy of alternating Bd and Ld treatments in elderly patients with NDMM.

We hypothesized that the study treatment would be effective because patients would receive first-line therapy with drugs of different mechanisms of action during each cycle; this would suppress the myeloma cells while reducing severe toxicity. Our results did not support the hypothesis in terms of efficacy, as the ORR, the primary endpoint, was 80.0% in this study, and its lower limit of 90% CI was below the threshold value of 70.4%. However, the 2-year PFS and OS of 40.0% and 80.0%, respectively, were comparable to those reported in elderly patients in the FIRST trial<sup>14</sup> or the UPFRONT study,<sup>15</sup> despite this MARBLE trial having 55.6% of patients with high-risk cytogenetics. Further, with respect to toxicity, the incidence of hematologic and non-hematologic AEs or serious AEs was similar to that reported previously.<sup>7,14</sup> Because Ld was approved in our country after the start of this study, it was not possible to enroll the planned number of patients in this study, and the study was discontinued early.

All patients received at least three cycles of Bd/Ld treatment, and 70.0% of them completed six cycles (54 weeks), suggesting that this study treatment was well-tolerated even in elderly patients with MM.<sup>7</sup> Further, considering that our study was aimed at patients aged over 75 years and that 70.0% of these patients completed the study treatment, our results for AEs are better than those reported in previous studies with elderly patients.<sup>7,14</sup>

Moreover, the treatment of patients aged 75 years or more needs to be optimized. Although the number of subjects was too small to draw any conclusions from this study, the alternating chemotherapy strategy based on a combination of proteasome inhibitors and IMiDs still has the potential to become one of the treatment options for elderly MM patients. This strategy can be applied in combination with anti-CD38 monoclonal antibodies.

The Bd/Ld alternating therapy is widely indicated in patients with standard-risk (other than high-risk subgroup), who face difficulty in using a combination of proteasome inhibitors and IMiDs owing to AEs and who can visit the hospital to receive Bd therapy once a week.

To summarize, the study suggests that alternating Bd/Ld treatment might be tolerable in elderly patients with NDMM; however, its efficacy was not determined because the number of patients was smaller than planned.

## AUTHOR CONTRIBUTIONS

AY and AK equally contributed to this work.

## ACKNOWLEDGEMENTS

This study was supported by an operating expense grant for research from the National Hospital Organization.

## DECLARATIONS

*Statement of ethics*

Written informed consent was obtained from every participant in the study.

This trial was approved by the Central Ethics Review Committee for Clinical Research of the National Hospital Organization on July 20, 2014 (H26-0320002).

*Conflicts of interest statement*

AK reports personal fees from Bayer Yakuhin, Ltd., as a member of the independent data monitoring committee of clinical trials outside the submitted work. KS received research funding from Ono Pharmaceutical, MSD, Celgene, AbbVie, Takeda Pharmaceutical, Sanofi, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Alexion Pharma, and GlaxoSmithKline and received honoraria from Ono Pharmaceutical, Celgene, Takeda Pharmaceutical, and Bristol-Myers Squibb. The other authors have no conflicts of interest to declare.

*Funding sources*

This study was supported by an operating expense grant for research from the National Hospital Organization.

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