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Original Article

# A Phase II Study to Evaluate the Efficacy of Bortezomib in Combination with Thalidomide in Treatment-Naïve Waldenstrom Macroglobulinemia Patients

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**Purpose** Despite the recent success of Bruton's tyrosine kinase (BTK) inhibitors for the treatment of Waldenstrom macroglobulinemia (WM), their indefinite treatment duration ultimately tantamount to substantial financial and emotional burden. On the other hand, fixed duration of proteasome inhibitors (PI) have shown rapid and reasonable response in WM treatment. Despite the well-known synergism between PI and immunomodulatory drugs (IMiD), there is no trials evaluating such combination in WM.

**Materials and Methods** Based on above, we designed this phase II study to investigate the efficacy and safety of 6 cycles of 28-day bortezomib-thalidomide-dexamethasone (VTD) regimen for treatment-naïve WM.

**Results** A total of 15 patients were enrolled: major response rate was 64.3%, and overall response rate was 78.6%. During the median follow-up of 41 months, median progression-free survival (PFS) was 13 months and overall survival 40 months. For responders, median duration of response was 13 months and median PFS 19 months. The most common adverse event (AE) of any grade was constipation (57.1%). The most common grade ≥ 3 AE was anemia (21.4%).

**Conclusion** All in all, we hereby provide proof-of-concept that PI + IMiD may be an attractive backbone for fixed duration treatment. It should be noted that granting the same level of access to newer drugs globally is virtually impossible. Thus efforts to develop regimens using readily available drugs to yield similar or adequate treatment outcomes should not be disregarded. In this sense, we believe our study holds its place for its novelty and eloquently addresses achieving the daunting societal quest of health equity.

**Key words** Waldenstrom macroglobulinemia, Bortezomib, Thalidomide, Frontline

## Introduction

Waldenstrom macroglobulinemia (WM) is defined as lymphoplasmacytic lymphoma (LPL) associated with IgM monoclonal gammopathy, irrespective of the M protein size [1,2]. The treatment of goal of WM is to control disease without compromising quality of life by treatment-related adverse events (AEs) [3,4]. Bruton's tyrosine kinase (BTK) inhibitors, based on recent success of iNNOVATE and ASPEN trials [5,6], constitute the incumbent standard of care, but this class of drug is not without faults. The most obvious pitfall is the "until progression or intolerance" indefinite treatment duration, which tantamount to substantial financial and emotional burden [7]. Furthermore, since the drug cessation may lead to rebound syndrome with major constitutive symptoms in case of ibrutinib [8], physicians are not comfortable with offering fixed duration treatment.

The proteasome inhibitor (PI) bortezomib has proven effective for WM treatment by specifically targeting nuclear-factor κB, with minor toxicity profiles if given weekly [9,10]. On the other hand, thalidomide is an immunomodulatory drug (IMiD) with moderate response rates around 40% in WM treatment when used in combination with dexamethasone [11,12]. Despite the synergism between bortezomib and thalidomide, there are no trials evaluating the efficacy of PI in combination with IMiD for WM. As such, we designed this phase II study to investigate the efficacy and safety of fixed duration bortezomib-thalidomide-dexamethasone (VTD) regimen for treatment-naïve WM.

It is important to note that this study was initiated in 2017, when there was no established treatment for WM in Asia. It should also be taken into consideration that due to the relatively small number of patients, even in comparison with other ethnicities [13], there are no treatment options other than traditional cytotoxic chemotherapy (CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone) that are both approved and reimbursed in Korea to date. In terms of health equity, it is virtually impossible for everyone around the

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globe to have the same level of access to newer drugs. Thus, efforts to develop regimens using readily available drugs to yield similar or adequate treatment outcomes should not be disregarded. In this sense, we believe our study holds its place for its novelty and contribution to alleviating medical resource constraints.

## Materials and Methods

### 1. Study design overview

This open-label, multicenter, non-randomized phase II trial was carried out in two tertiary hospitals in Korea between December 2017 (first patient in after ClinicalTrials.gov registration) to December 2020 (ClinicalTrials.gov identifier: NCT03335098).

### 2. Study population and intervention

Patients older than 19 years with treatment-naive WM [14] were considered eligible for enrollment. Additionally, only the patients with ECOG (Eastern Cooperative Oncology Group) performance status of 0-2 and adequate bone marrow function, defined as absolute neutrophil count ≥ $1.0\times10^9$/L, platelet count ≥ $20\times10^9$/L, and hemoglobin ≥ 6.0 g/dL, were allowed to participate. Patients with pre-existing neuropathy ≥ grade 2 or hyperviscosity syndrome requiring plasmapheresis were excluded from the study. Patients with previous history of other types of hematologic malignancies, those with history of organ transplantation, and those with disease involving central nervous system were also deemed ineligible for the study.

Originally, patients were to undergo a 28-day treatment for 6 cycles; bortezomib 1.3 mg/m$^2$ on days 1, 4, 8, and 11; thalidomide 50 mg on days 1-28; and dexamethasone 40 mg (either orally or intravenously) on days 1-4. Weekly bortezomib administration (days 1, 8, 15, and 22) was also allowed per attending physician's choice.

Either aspirin or plavix was used as thrombophylaxis measurement with thalidomide administration. To prevent herpes zoster infection, either acyclovir 400 mg twice a day or valacyclovir 500 mg twice a day was given during bortezomib treatment.

### 3. End points and statistical analysis

The primary endpoint of the study was overall response rate (ORR) after completion of 6 cycles. ORR was defined as minor response (MR) or better response. The response evaluation was carried out per 6th International Workshop on WM [15,16] at the end of every cycle on day 28. Imaging (computed tomography scan) was done at the end of 3rd and 6th cycle for those with underlying adenopathy/organomegaly. Major response was defined as composite of complete response (CR)+very good partial response (VGPR)+partial response (PR).

The secondary endpoints included progression-free survival (PFS), overall survival (OS) and AE. The PFS was defined as time from study drug administration to relapse or death from any cause. The OS was defined from study drug administration to death of any cause. Patients were followed-up until January 2023. The AE were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.03.

The sample size was calculated based on Fleming Single Stage procedure. The assumption was that if the ORR rate was 84.7% [17], this would be considered effective. With a power of 80%, alpha=5% and 20% dropout rate, 15 patients were required.

Fisher's exact test was used for nominal variables, and Mann-Whitney U test was used for continuous variables. The survival curves were estimated using the Kaplan-Meier method. All data were analyzed using the Statistical Package for the Social Sciences software (IBM SPSS Statistics ver. 25.0, IBM Corp., Armonk, NY).

## Results

### 1. Baseline characteristics

The baseline characteristics of all patients are shown in Table 1. The median age at diagnosis was 68 years (range, 55 to 80 years), and the median serum IgM level was 3.3 g/dL. There were two patients (13.3%) with high R-IPSS(4) score and two with very high R-IPSS score (13.3%). *MYD88* mutation status was available in seven patients: all of them harbored *MYD88*$^{L265P}$ mutation. CXCR4 status was not checked. The median time to treatment initiation since diagnosis was 22 days (range, 8 to 426 days). Primary reasons for initiating treatment were B symptoms (n=7, 46.7%), cytopenias (n=5, 33.3%), and lymphadenopathy/organomegaly (n=3, 20%).

### 2. Treatment outcomes

One patient withdrew consent during cycle 1 due to undisclosed personal reasons and was lost to follow-up. Thus, treatment outcomes were evaluated in 14 out of 15 patients. Among them, 12 patients completed the planned 6 cycles, while one patient progressed after cycle 1 and one patient progressed after cycle 4 after initially achieving MR.

As shown in Table 2, there were no CR but 2 (14.3%) showed VGPR and 7 (50%) showed PR, cumulating to major response rate of 64.3%. There were two patients (14.3%) with MR, and including these 2, the ORR was 78.6%. The median time to best response was 6 months (range, 3 to 12 months).

**Table 1.** Patient characteristics of all patients (n=15)

| Characteristic | No. (%) |
|---|---|
| **Age (yr), median (range)** | 68 (55-80) |
| > 65 | 10 (66.7) |
| > 75 | 1 (6.7) |
| **Male sex** | 10 (66.7) |
| **R-IPSS WM** | |
| Low | 5 (33.3) |
| Intermediate | 6 (40.0) |
| High | 2 (13.3) |
| Very high | 2 (13.3) |
| **ECOG** | |
| 0 | 1 (6.7) |
| 1 | 8 (53.3) |
| 2 | 6 (40.0) |
| **Lymphadenopathy** | 11 (73.3) |
| **Splenomegaly** | 7 (46.7) |
| **Bone marrow involvement** | 15 (100) |
| Lymphocytes (%), median (range) | 28.3 (12.2-93.8) |
| **IgM (g/dL), median (range)** | 3.3 (0.4-5.9) |
| ≥ 3.3 | 5 (33.3) |
| < 3.3 | 10 (66.7) |
| **β-2 microglobulin (mg/L), median (range)** | 4.5 (1.9-9.7) |
| **Cytopenia at baseline** | |
| Hemoglobin ≤ 11 g/dL | 10 (66.7) |
| Platelet ≤ $100\times10^9$/L | 3 (20.0) |
| Absolute neutrophil count ≤ $1.5\times10^9$/L | 2 (13.3) |
| *MYD88*$^{L265P}$ | 7/7 (100) |

ECOG, Eastern Cooperative Oncology Group; R-IPSS, revised international prognostic score system (4); WM, Waldenstrom macroglobulinemia.

**Table 2.** Treatment outcomes

| Outcome | No. (%) |
|---|---|
| **Best overall response** | |
| CR | 0 |
| VGPR | 2 (14.3) |
| PR | 7 (50.0) |
| MR | 2 (14.3) |
| SD | 2 (14.3) |
| PD | 1 (7.1) |
| Not evaluable | 1 (7.1) |
| **Response rates** | |
| VGPR/CR | 2 (14.3) |
| MRR | 9 (64.3) |
| ORR | 11 (78.6) |
| **Death** | 2 (14.3) |
| Disease progression | 2 |

CR, complete response; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

There were no incidences of tumor flare after treatment cessation.

During the median follow-up of 41 months, all but two patients experienced disease progression or died (2 deaths due to disease progression, 10 disease progressions). Of the 10 patients who experienced disease progression, seven patients went onto received rituximab-based treatment (bendamustine-rituximab in 5, cyclophosphamide-rituximab-steroids in 2). Four out of these seven patients remained in remission up until the data-cutoff, while one progressed while on rituximab and died due to disease progression, one relapsed and went on to receive zanubrutinib, and the last one relapsed and underwent bendamustine-rituximab re-treatment. Of the 10 patients who experienced disease progression, the other three went onto receive BTK inhibitors. The four patients subjected to BTK inhibitors (3 zanubrutinib, 1 pirtobrutinib) was on treatment up until the data-cutoff.

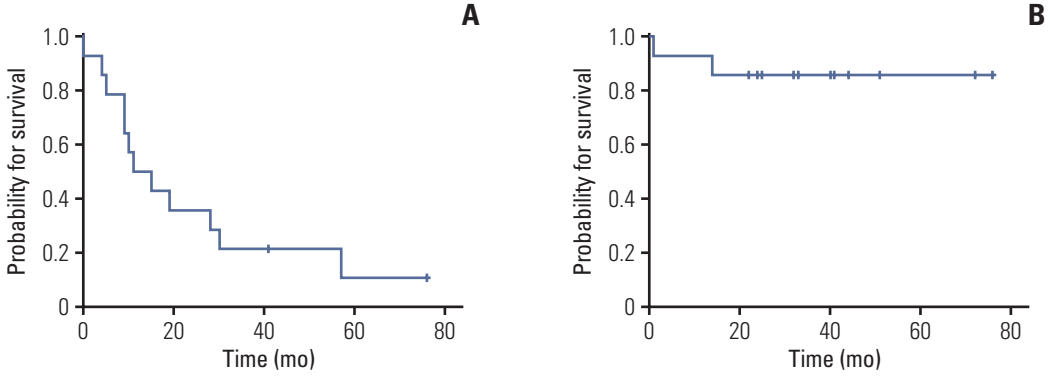


**Fig. 1.** (A) Progression-free survival. (B) Overall survival.

**Table 3.** Adverse events in 14 patients who underwent at least 1 cycle of VTD

| Event term | Any | Grade ≥ 3 |
|---|---|---|
| **Hematologic** | | |
| Neutropenia | 2 (14.3) | 2 (14.3) |
| Anemia | 4 (28.6) | 3 (21.4) |
| Thrombocytopenia | 3 (21.4) | 1 (7.1) |
| **Non-hematologic** | | |
| Peripheral neuropathy | 6 (42.9) | 0 |
| Constipation | 8 (57.1) | 1 (7.1) |
| Skin rash | 2 (14.3) | 0 |
| Fatigue | 1 (7.1) | 1 (7.1) |
| **Documented infection** | | |
| Viral | 0 | |
| Bacterial | 3 (21.4) | |
| Fungal | 0 | |
| **Dose reduction** | | |
| Bortezomib | 6 (42.9) | |
| Thalidomide | 0 | |
| **Dose delay** | 4 (28.6) | |

VTD, bortezomib-thalidomide-dexamethasone.

The median PFS was 13 months and the OS not reached (Fig. 1). For patients achieving MR or better response, the median duration of response was 13 months and median PFS 19 months.

### 3. Adverse events

AEs were captured in 14 patients who completed at least 1 full cycle of VTD (Table 3). The most common AE of any grades was constipation (57.1%). The most common grade ≥ 3 AE was anemia (21.4%). Bortezomib dose modification occurred in six patients due to neuropathy (2/6), infection (2/6), cytopenia (1/6), and skin rash (1/6). Five out of six patients received bortezomib –1 level dose, and one received –2 level dose. There was one case of thalidomide dose reduction on top of bortezomib dose reduction due to infection. Dose reduction was not associated with diminished response to the treatment (major response rate [MRR] 4/6, 66.7% vs. 5/8 62.5%; ORR 5/6, 83.3% vs. 6/8, 75%). There were three cases of documented bacterial infection: one after cycle 1, one after cycle 2, and one after cycle 6. There were no cases of viral or fungal infection. There were no cases of thromboembolism events.

## Discussion

Here, we report the results of the first trial investigating the outcomes of PI+IMiD combination therapy for treatment-naïve WM. In terms of ORR (78.6%), our regimen seems slightly less effective as all the previous studies reported ORR ≥ 80% (84.7% to 88.5%). Because our original assumption was that bortezomib+thalidomide+dexamethasone would incur ORR of 84.7%, our results did not reach the planned goal. However, it is noteworthy that with MRR of 64.3%, bortezomib+thalidomide+dexamethasone showed similar MRR compared to previous rituximab+bortezomib based treatments with ranging MRR from 65.4% to 69.9% (Table 4). Also, considering the fact that the median time to response was 6 months (range, 3 to 12 months) and the disease dynamics, we acknowledge that longer treatment duration might have been more beneficial and measurement of ORR at a later stage more scientifically relevant.

Per National Comprehensive Cancer Network guidelines [18], the current category 1 therapy for treatment naïve WM/LPL is the BTK inhibitors. While it is true that MRR of fixed duration therapy is lower than that of ibrutinib (77%) or zanubrutinib (78%) [6], the clear advantage of shortened treatment duration cannot be disregarded. Also, since the previous exposure to VTD does not negatively affect the subsequent BTK inhibitor treatment, we believe it is reasonable to sequence the BTK inhibitor treatment after the fixed duration therapy. In our experience, there were four patients would ultimately went on to receive either zanubrutinib or

**Table 4.** Previous clinical trials of fixed duration treatment for previously untreated WM

| | Study design | Total patients | Treatment | MRR (%) | ORR (%) |
|---|---|---|---|---|---|
| Current study | Phase II, single arm | 15 | Bortezomib+thalidomide+dexamethasone | 64.8 | 78.6 |
| Treon et al. [19][a)] | Phase II, single arm | 25 | Rituximab+thalidomide | 64 | 72 |
| Ghobrial et al. [9] | Phase II, single arm | 26 | Rituximab+bortezomib | 65.4 | 88.5 |
| Dimopoulos et al. [17] | Phase II, single arm | 59 | Rituximab+bortezomib+dexamethasone | 67.8 | 84.7 |
| Buske et al. [20] | Phase III, RCT | 100 | Rituximab+bortezomib+cyclophosphamide +dexamethasone | 80.6 | 94.6 |
| | | 100 | Rituximab+cyclophosphamide+dexamethasone | 69.9 | 86.7 |

MRR, major response rate; ORR, overall response rate; RCT, randomized controlled trial; WM, Waldenstrom macroglobulinemia. [a)]This trial included both previously untreated (n=20) and relapsed/refractory (n=5) patients.

pirtobrutinib, and all of them achieved MRR.

As for the recent quadruplet therapy using rituximab, bortezomib, cyclophosphamide and dexamethasone (B-DRC), one should note that although B-DRC (MRR 80.6%) showed better response compared to DRC (MRR 69.9%), this clinical benefit did not translate into survival gain [20]. In the era of emerging novel therapies such as bispecifics, preserving T cell repertoire is especially important. In this sense chemotherapy free regimen is always preferred over cytotoxic agents use. On the other hand, rituximab is associated with prolonged B cell depletion and secondary hypogammaglobulinemia [21]. Rituximab may dampen humoral response and therefore increase the risk of infection complications [22], and this was especially relevant during the pandemic. As such, our chemo-free, antibody-free VTD regimen may be hold some advantage in certain settings—especially for patients with concurrent amyloidosis.

We acknowledge that our bortezomib schedule might be the culprit for higher rates of peripheral neuropathy and dose reduction. For rapid tumor shrinkage purpose, all patients underwent twice weekly bortezomib schedule for cycle 1. However, per attending physician's decision, weekly bortezomib schedule was also allowed from subsequent cycles.

One of the most obvious limitations of this study is the small number of patients. However, it is worth noting that this trial is followed by a companion Korean multi-center phase II trial (NCT03697356, BALLONDOR) investigating the efficacy of rituximab in combination with bortezomib-lenalidomide-dexamethasone for treatment-naïve WM. In the subsequent BALLONDOR trial, 54 patients have been enrolled: the results of this study is expected to answer some of the questions not addressed by ours such as the optimal bortezomib dose and delivery schedule and the mutation status on the treatment outcomes. Specifically, *MYD88* mutation status was available in only seven patients in our study and *CXCR4* in none. Although we do not believe this negatively affected our study as *MYD88* mutation status is not related survival or response to immunochemotherapy [23], there is a need for better understanding on the relationship between mutational landscape and response to PIs.

All in all, we hereby provide proof-of-concept that PI+IMiD combination may be an attractive backbone for fixed duration treatment of previously untreated WM. Also, we believe our study eloquently addresses achieving the daunting societal quest of health equity: for physicians, re-discovery of relatively accessible drugs can be the simplest step towards fixing the ever-growing disparities.

**Ethical Statement**

The study was conducted according to the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital (H-1605-137-765). Informed consent was taken from all patients before participating in any study-related procedure.

**Author Contributions**

Conceived and designed the analysis: Byun JM, Shin J, Yoon SS, Koh Y.
Collected the data: Byun JM, Kim SA, Park H, Lee J, Shin DY, Hong J, Lee JO, Bang SM, Kim I, Yoon SS, Koh Y.
Contributed data or analysis tools: Byun JM, Kim SA, Park H, Lee J, Shin DY, Hong J, Lee JO, Bang SM, Kim I, Yoon SS, Koh Y.
Performed the analysis: Byun JM, Koh Y.
Wrote the paper: Byun JM, Koh Y.
Reviewed the paper: Shin J, Kim SA, Park H, Lee J, Shin DY, Hong J, Lee JO, Bang SM, Kim I, Yoon SS.

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**Conflicts of Interest**

Bortezomib (Velkin®) was provided by Boryung Pharmaceutical Co.

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