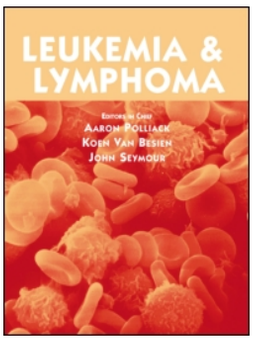

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ORIGINAL ARTICLE

Phase 3 study of subcutaneous bortezomib, thalidomide, and prednisolone consolidation after subcutaneous bortezomib-based induction and autologous stem cell transplantation in patients with previously untreated multiple myeloma: the VCAT study

Noemi Horvath[a], Andrew Spencer[b], Melita Kenealy[c], Douglas Joshua[d], Philip J Campbell[e], Je-Jung Lee[f], Jian Hou[g], Lugui Qiu[h], Anna Kalff[b], Tiffany Khong[b], Anil Londhe[i], Sarah Siggins[j], Maximiliano van Kooten Losio[j], Michael Eisbacher[j] and H. Miles Prince[c,k]

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ABSTRACT

Efficacy and safety of bortezomib-based consolidation following ASCT were investigated in newly diagnosed multiple myeloma patients from Australia, Korea, and China. Patients received three cycles of bortezomib-cyclophosphamide-dexamethasone induction followed by high-dose therapy/ASCT, then were randomized (1:1) to consolidation with TP (thalidomide 100 mg/d for ≤12 months/until disease progression; prednisolone 50 mg on alternate days indefinitely/until disease progression; $n = 100$) or VTP (subcutaneous bortezomib 1.3 mg/m^2 every 2 weeks for 32 weeks, plus TP; $n = 103$). The hypothesized difference in CR + VGPR rate (after ≤12 months consolidation therapy) was not met. The rate of CR + VGPR was numerically higher with VTP versus TP; however, this was not statistically significant (85.7% versus 77.1%; rate difference 8.6%; 95% confidence interval −2.3%–19.5%; $p = .122$). Secondary efficacy outcomes were similar between treatment arms. Addition of bortezomib to TP consolidation was associated with limited additional toxicity but did not significantly improve efficacy versus TP.

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Bortezomib; multiple myeloma; consolidation; phase 3

Introduction

Development of novel therapeutic agents such as proteasome inhibitors and immunomodulatory drugs (IMiDs), and the combination of these agents with existing therapies, has significantly improved response rates and survival outcomes for patients with multiple myeloma (MM) in recent years [1–3]. High-dose therapy (HDT) plus autologous stem cell transplant (ASCT) represents a standard of care among eligible patients with newly diagnosed MM (NDMM); patients typically receive triplet induction therapy prior to ASCT, followed by consolidation and/or maintenance therapy [4,5]. Several studies have shown that achievement of complete response (CR) or very good partial response (VGPR) before and after ASCT is strongly associated with improved clinical outcomes [6–8], thus supporting the concept of post-ASCT consolidation treatment.

In Australia, to date, the standard of care post-ASCT has been 12 months of thalidomide combined with indefinite prednisolone (TP). This is based on the demonstrated superiority of TP over prednisolone alone for both progression-free survival (PFS) and overall survival (OS) [9,10]. In light of these results, post-ASCT TP has been routinely used in Australia and elsewhere [11].

The use of bortezomib-based consolidation therapy post-ASCT has been shown to deepen responses and prolong PFS [12–14]. Such consolidation has been

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Supplemental data for this article is available online at here.

reported to provide meaningful response benefits for patients with NDMM. Specifically, a phase 3 study compared post-ASCT consolidation with bortezomib-thalidomide-dexamethasone (VTD) after VTD induction versus thalidomide-dexamethasone (TD) after TD induction; the efficacy of consolidation therapy was improved with VTD versus TD [15]. VTD consolidation was also evaluated in a study of patients with MM responding to ASCT, in whom it induced persistent molecular remission in a proportion of patients [12]. In another phase 3 study, single-agent bortezomib consolidation significantly improved PFS compared with a control group receiving no consolidation [13].

This study was designed to assess whether the addition of subcutaneous (SC) bortezomib to post-ASCT consolidation with TP improved responses and outcomes in patients with NDMM when *all* patients had received SC bortezomib with oral cyclophosphamide and dexamethasone (VCD) induction.

Methods

Study design

This randomized, open-label, phase 3 study was conducted at sites in Australia, China, and Korea (14, 3, and 5 sites, respectively) from January 2012 to January 2016. The study comprised six phases: screening, induction treatment, peripheral blood stem cell (PBSC) collection and ASCT, randomization, consolidation, and follow-up.

After screening, eligible patients received three 21-d cycles of VCD induction (SC bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; oral cyclophosphamide 300 mg/m^2 on days 1, 8, and 15; oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12) followed by PBSC mobilization and collection. Patients with adequate PBSC collection and no contraindication to HDT with intravenous melphalan 200 mg/m^2 and ASCT then proceeded to HDT/ASCT.

Patients with no evidence of progressive disease (PD) 30–50 d post-ASCT were centrally randomized (1:1) based on a computer-generated randomization schedule to consolidation with TP (thalidomide 100 mg/d, for a maximum of 12 months or until PD, whichever occurred first; prednisolone 50 mg on alternate days, continued indefinitely or until PD) or VTP (SC bortezomib 1.3 mg/m^2 every 2 weeks for 32 weeks, plus TP).

Randomization was stratified by International Staging System (ISS) stage at diagnosis (I versus II versus III), response post-ASCT (CR versus VGPR versus partial response versus stable disease) per investigator assessment, and cytogenetic risk (high-risk versus low-risk versus unknown). Patients were followed for 3 years post-randomization.

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki, in line with Good Clinical Practice and applicable local guidelines. All study documents were approved by an Independent Ethics Committee or Institutional Review Board at all study sites. All patients provided informed, written consent.

Patients

Eligible patients were aged ≥18 years and had a diagnosis of MM based on International Myeloma Working Group (IMWG) criteria (see also Supplementary methods) [16]. Patients were also required to be eligible for ASCT in line with local institutional guidelines. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2, and adequate hematologic, renal, and hepatic function. Key exclusion criteria are outlined in the Supplementary methods.

Endpoints

The primary endpoint was the proportion of post-ASCT, response-evaluable patients who achieved CR + VGPR (≥VGPR) as their best response after up to 12 months of consolidation therapy. Secondary endpoints were: CR rate and stringent CR (sCR) rate at 3, 6, 9, and 12 months of consolidation in response-evaluable patients, PFS from randomization, disease-free survival (DFS; applied only to patients in CR), OS from randomization, overall response rate (ORR) to VCD induction and to ASCT (for all patients who received bortezomib, irrespective of whether or not they proceeded to randomization and consolidation), safety and tolerability, health-related quality of life (HRQoL), and patient-reported symptoms of peripheral neuropathy (PN).

Assessments

The study used local laboratory tests. Response to therapy and disease progression was evaluated per IMWG Uniform Response Criteria for MM [16] and was calculated using a computer algorithm based on values entered into the electronic case report form. Safety was assessed throughout the study via the incidence of treatment-emergent adverse events (TEAEs) per National Cancer Institute Common Terminology

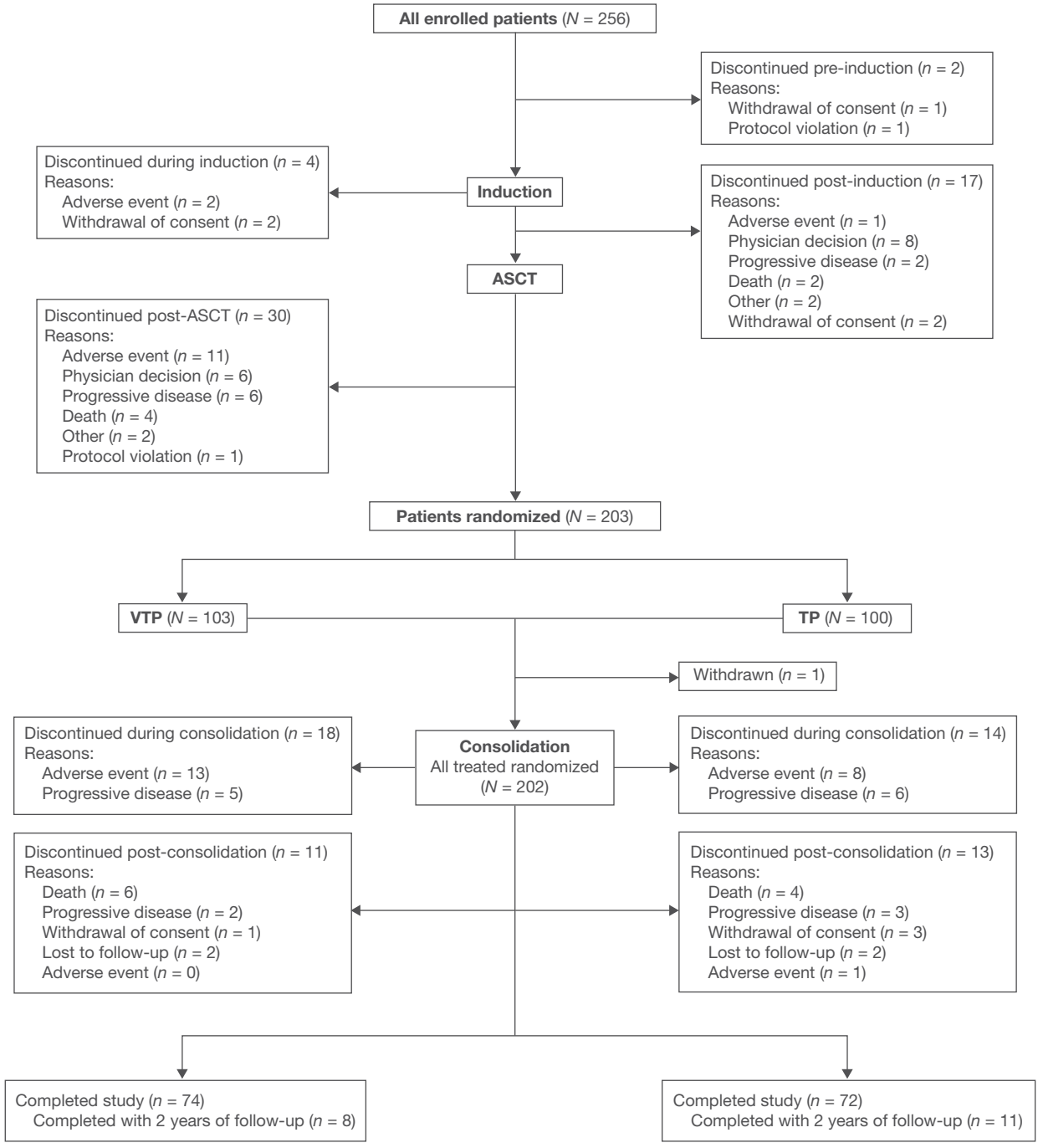

Figure 1. Patient disposition (CONSORT diagram). ASCT: autologous stem cell transplantation; TP: thalidomide-prednisolone; VTP: bortezomib-thalidomide-prednisolone.

Criteria for Adverse Events (NCI CTCAE) v4.03. Further details of assessments conducted are provided in the Supplementary methods.

Statistical analysis

Statistical analyses are summarized in the Supplementary methods.

Results

Patient characteristics and study flow

In total, 256 patients were enrolled in the study. Of these, 254 received VCD induction, 233 underwent ASCT, and 203 patients were randomized, 103 to VTP consolidation and 100 patients to TP consolidation (Figure 1). Fifty three patients discontinued prior to

Table 1. Patient demographics and disease characteristics at baseline for patients randomized to VTP or TP consolidation (all-randomized-analysis set).

		All-randomized	
	All-enrolled ($N = 256$)	VTP ($N = 103$)	TP ($N = 100$)
Age, years			
Median	59.0	58.0	58.0
Range	32–71	34–71	32–71
18–<65 years, *n* (%)	207 (80.9)	88 (85.4)	81 (81.0)
≥65 years, *n* (%)	41 (19.1)	15 (14.6)	19 (19.0)
Male/female, *n* (%)	147 (57)/109 (42.6)	53 (51)/50 (49)	57 (57)/43 (43)
Race, *n* (%)			
White	185 (72)	72 (70)	75 (75)
Asian	58 (23)	23 (22)	21 (21)
Other	4 (2)	2 (2)	1 (1)
Unknown/ot reported	9 (4)	6 (6)	3 (3)
ECOG PS, *n* (%)			
0	115 (45)	51 (50)	43 (43)
1	122 (48)	46 (45)	50 (50)
2	17 (7)	6 (6)	7 (7)
ISS staging, *n* (%)			
I	85 (33)	33 (32)	35 (35)
II	123 (48)	52 (50)	48 (48)
III	46 (18)	18 (17)	17 (17)
Missing/unknown	2 (1)	0	0
Cytogenetic risk[a]			
High	53 (21)	24 (23)	23 (23)
Low	175 (68)	68 (66)	67 (67)
Unknown	28 (11)	11 (11)	10 (10)
Type of MM[b]	256 (100)	103 (100)	100 (100)
Non-secretory	5 (2)	4 (4)	1 (1)
Oligosecretory	7 (3)	4 (4)	3 (3)
Secretory	244 (95)	95 (92)	96 (96)
Creatinine at baseline (μmol/L), *n* (%)			
>ULN	38 (15)	9 (9)	17 (17)
≤ULN	216 (85)	94 (91)	83 (83)

ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; MM: multiple myeloma; SD: standard deviation; TP: thalidomide-prednisolone; ULN: upper limit of normal; VTP: bortezomib-thalidomide-prednisolone.

[a]Cytogenetic risk was assessed by FISH and/or karyotyping with abnormalities t(4;14), del17p, amp1q, and t(14;16) identifying high risk.

[b]All patients who were enrolled were required to have at least one of the following: serum M-protein ≥1 g/dL (≥10 g/L); urine M-protein ≥200 mg/24 h; or, serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) provided serum FLC ratio was abnormal. All patients met this criterion; the classification of patients as having non-secretory (specifically those without detectable M-protein in the blood or urine) or oligosecretory (specifically those with M-protein levels in the blood or urine that were too low to measure changes accurately over time) myeloma was as reported by the investigators.

randomization (pre-induction, $n = 2$; during induction, $n = 4$, post-induction, $n = 17$; post-ASCT, $n = 30$). Baseline demographics and disease characteristics (before start of induction) of all-enrolled and all-randomized patients are shown in Table 1. Median age for the intent-to-treat population was 59 years (range 32–71 years; 19.1% >65 years). Fifteen percent of patients had creatinine above the upper limit of normal; 4.7% had oligosecretory or non-secretory disease. Cytogenetic risk was assessed in 90% of patients with 20.7% considered to have high-risk cytogenetics. Patient characteristics were generally similar between VTP and TP groups (Table 1).

Response

Of the 254 patients who received induction therapy, 243 were evaluable for response. The percentage of patients who achieved ≥VGPR as their best response (per computer algorithm assessment) by the end of induction was 18.1% (ORR = 71.6%) (Table 2). By the end of the ASCT phase, the percentage of patients who achieved ≥VGPR as their best response was 35.8% (2.5% CR, ORR = 79%). Eight patients (3.1%) developed PD either during induction or post-transplant. At randomization, the rate of ≥VGPR (VTP versus TP; per computer algorithm assessment) was 42.9% versus 37.5% (CR 2% versus 4.2%).

After randomization, the percentage of patients achieving ≥VGPR (VTP versus TP) during consolidation treatment was increased at 3 months (69% versus 65%) and at 9 months (86% versus 77%), and was maintained at 12 months – the primary endpoint of this study (85.7% versus 77.1%; rate difference 8.6%; 95% CI −2.3% to 19.5%; $p = .122$) (Table 3). Figure 2

shows subgroup analyses of ≥ VGPR after 12 months' consolidation; the study was not statistically designed to show significant differences between subgroups. Consistent with the analysis of the primary endpoint, the percentage of patients achieving ≥ VGPR was numerically higher with VTP versus TP in most of the subgroups analyzed, including 96.0% ($n = 24/25$) versus 78.3% ($n = 18/23$) in the subgroup of patients with high-risk cytogenetics.

Median duration of response (DoR) for responders to consolidation therapy (VTP: $n = 95$; TP: $n = 93$) in the all response-evaluable-randomized analysis set was not reached in either treatment arm (48 DoR events; HR 1.042; 95% CI 0.591–1.837; $p = .8879$). In the VTP and TP groups, respectively, 84.7% and 81.8% of responders remained in response after 18 months, and 54.2% and 53.0% after 36 months.

After 12 months of consolidation, the proportion of patients with no evidence of minimal residual disease was 20.4% in the VTP group and 20.8% in the TP group (20 patients in each group; rate difference −0.4%; 95% CI −11.8% to 11.0%).

Table 2. Best response rates pre-randomization per computer algorithm assessment (all-treated-evaluable population[a]).

n (%)	Induction/PBSC/ ASCT ($N = 243$)	95% CI for response
Post-induction[a]		
≥VGPR	44 (18.1%)	(13.5%, 23.5%)
CR	0	NA
VGPR	44 (18.1%)	(13.5%, 23.5%)
PR	130 (53.5%)	(47.0%, 59.9%)
SD	69 (28.4%)	(22.8%, 34.5%)
Post-ASCT[b]		
≥VGPR	87 (35.8%)	(29.8%, 42.2%)
CR	6 (2.5%)	(0.9%, 5.3%)
VGPR	81 (33.3%)	(27.4%, 39.6%)
PR	106 (43.6%)	(37.3%, 50.1%)
SD	50 (20.6%)	(15.7%, 26.2%)

ASCT: autologous stem cell transplantation; CI: confidence interval; CR: complete response; PBSC: peripheral blood stem cell collection; PR: partial response; SD: stable disease; VGPR: very good partial response.
[a]Patients who received at least 1 dose of study drug and had at least one response assessment performed.
[b]Patients who did not undergo ASCT had their best responses carried forward.

Survival

Median follow-up post-randomization for PFS was 22.3 months in the VTP arm and 23.2 months in the TP arm. Based on 59 PFS events (VTP: 31 [67 censored]; TP: 28 [68 censored]), the median PFS was 31.7 months in the VTP arm and 32.8 months in the TP arm (HR 1.12; 95% CI 0.67–1.87; $p = .6689$) (Figure 3(A)). Twelve-month PFS rates in the VTP and TP arms, respectively, were 89.7% and 86.4% and 24-month PFS rates were 65.5% and 74.2%. Eleven patients developed PD during consolidation therapy (five patients on the VTP arm; six patients on the TP arm).

At data cutoff, OS data were not yet mature (10 events). Based on 44 DFS events (VTP: 24; TP: 20), median DFS for complete responders (VTP: $n = 39$; TP: $n = 43$) was 11.2 months in the VTP arm and 16.4 months in the TP arm (HR 1.46; 95% CI 0.80–2.65; $p = .2107$) (Figure 3(B)). Twelve-month DFS rates were 44.0% in the VTP arm and 61.9% in the TP arm, and 30-month DFS rates were 28.0% and 33.6%, respectively.

Table 3. Cumulative best response rates from randomization per computer algorithm assessment (all-randomized-evaluable population).

	Phase of study					
		Consolidation				
n (%)	At randomization[a]	3 months	6 months	9 months	12 months	At follow-up
VTP arm ($n = 98$)						
≥VGPR	42 (42.9)	68 (69.4)	78 (79.6)	84 (85.7)	84 (85.7)	84 (85.7)
CR	2 (2.0)	15 (15.3)	23 (23.5)	30 (30.6)	30 (30.6)	39 (39.8)
VGPR	40 (40.8)	53 (54.1)	55 (56.1)	54 (55.1)	54 (55.1)	45 (45.9)
PR	41 (41.8)	26 (26.5)	17 (17.3)	11 (11.2)	11 (11.2)	11 (11.2)
SD	15 (15.3)	4 (4.1)	3 (3.1)	3 (3.1)	3 (3.1)	3 (3.1)
TP arm ($n = 96$)						
≥VGPR	36 (37.5)	62 (64.6)	68 (70.8)	74 (77.1)	74 (77.1)	75 (78.1)
CR	4 (4.2)	22 (22.9)	27 (28.1)	30 (31.3)	31 (32.3)	43 (44.8)
VGPR	32 (33.3)	40 (41.7)	41 (42.7)	44 (45.8)	43 (44.8)	32 (33.3)
PR	45 (46.9)	30 (31.3)	25 (26.0)	19 (19.8)	19 (19.8)	18 (18.8)
SD	15 (15.6)	4 (4.2)	3 (3.1)	3 (3.1)	3 (3.1)	3 (3.1)

CR: complete response; HDT/ASCT: high-dose therapy/autologous stem cell transplantation; PR: partial response; SD: stable disease; TP: thalidomide-prednisolone; VGPR: very good partial response; VTP: bortezomib-thalidomide-prednisolone.
[a]Response post-HDT/ASCT in the response-evaluable population at randomization per computer algorithm assessment.

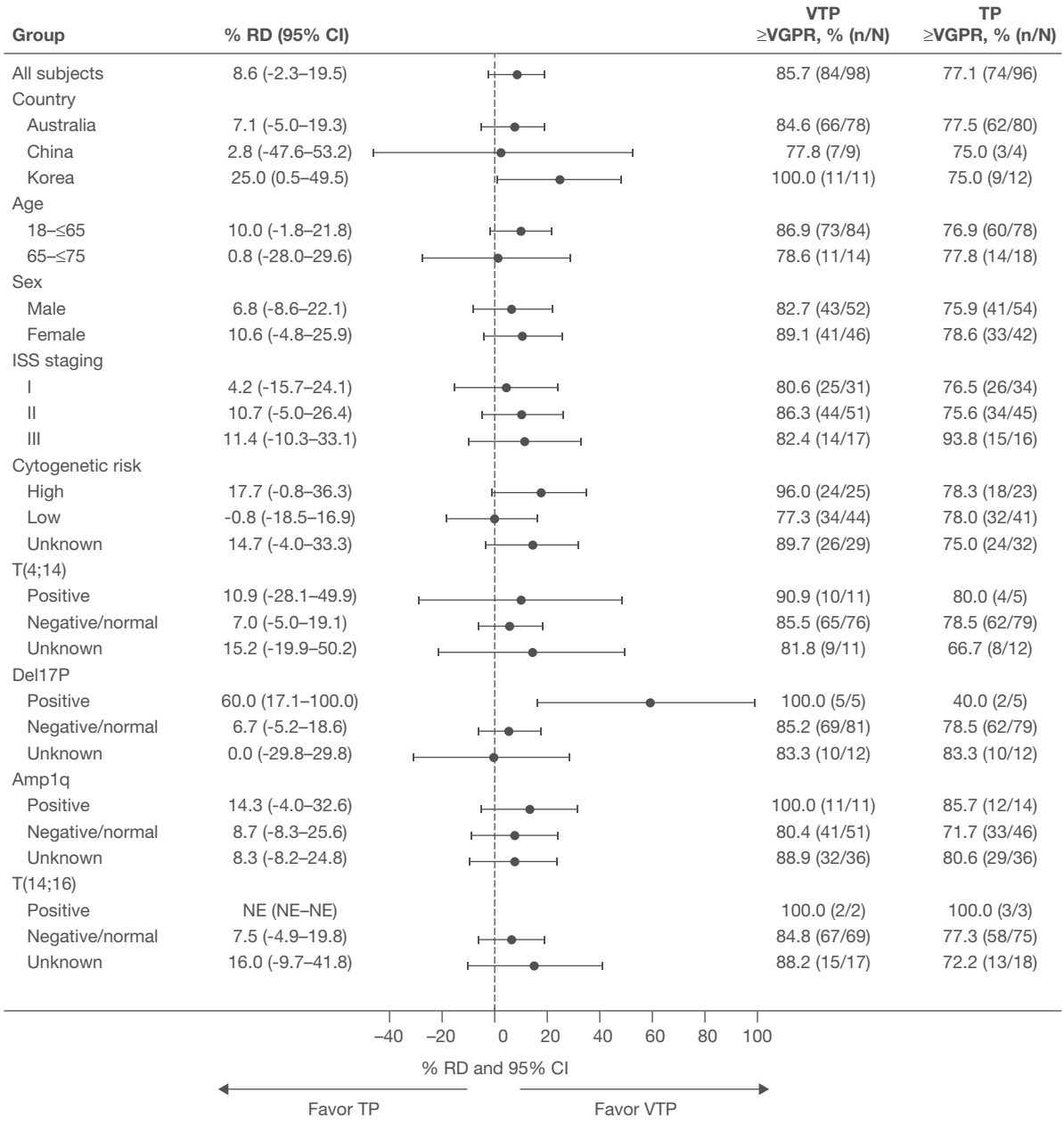

Figure 2. Subgroup analyses of overall best response (≥VGPR) after 12 months of consolidation therapy per computer algorithm assessment (all subgroups except 'Country' were pre-specified). ASCT: autologous stem cell transplantation; CI: confidence interval; CR: complete response; ISS: International Staging System; NE: not evaluable; RD: rate difference; PR: partial response; TP: thalidomide-prednisolone; VGPR: very good partial response; VTP: bortezomib-thalidomide-prednisolone.

Safety

During VCD induction ($n = 254$; median three cycles; mean dose intensity 98.68%), 245 patients (96%) experienced ≥1 TEAE, and 216 patients (85%) had a TEAE considered to be drug-related. The most common TEAEs (of any grade) were infection ($n = 103$, 40.6%), constipation ($n = 92$, 36.2%), and nausea ($n = 82$, 32.3%). Grade ≥3 TEAEs were reported in 107 patients (42%); the most common was neutropenia ($n = 15$; 6%). Of note, PN not elsewhere classified (NEC) (system organ class comprising peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and neuritis) occurred in 100 patients (39%) in the induction phase; however, most events were grade 1 or 2 ($n = 91$, 36%); grade 3 PN was reported in nine patients (3.5%).

During consolidation, median duration of bortezomib treatment in the VTP arm was 6.9 months (range 0–8.4) and the mean (SD) relative dose intensity was 96.7% (6.52). The median duration of thalidomide treatment was 10.2 months (range 0–11.1) in the VTP arm and 10.1 months (0–13.8) in the TP arm. The

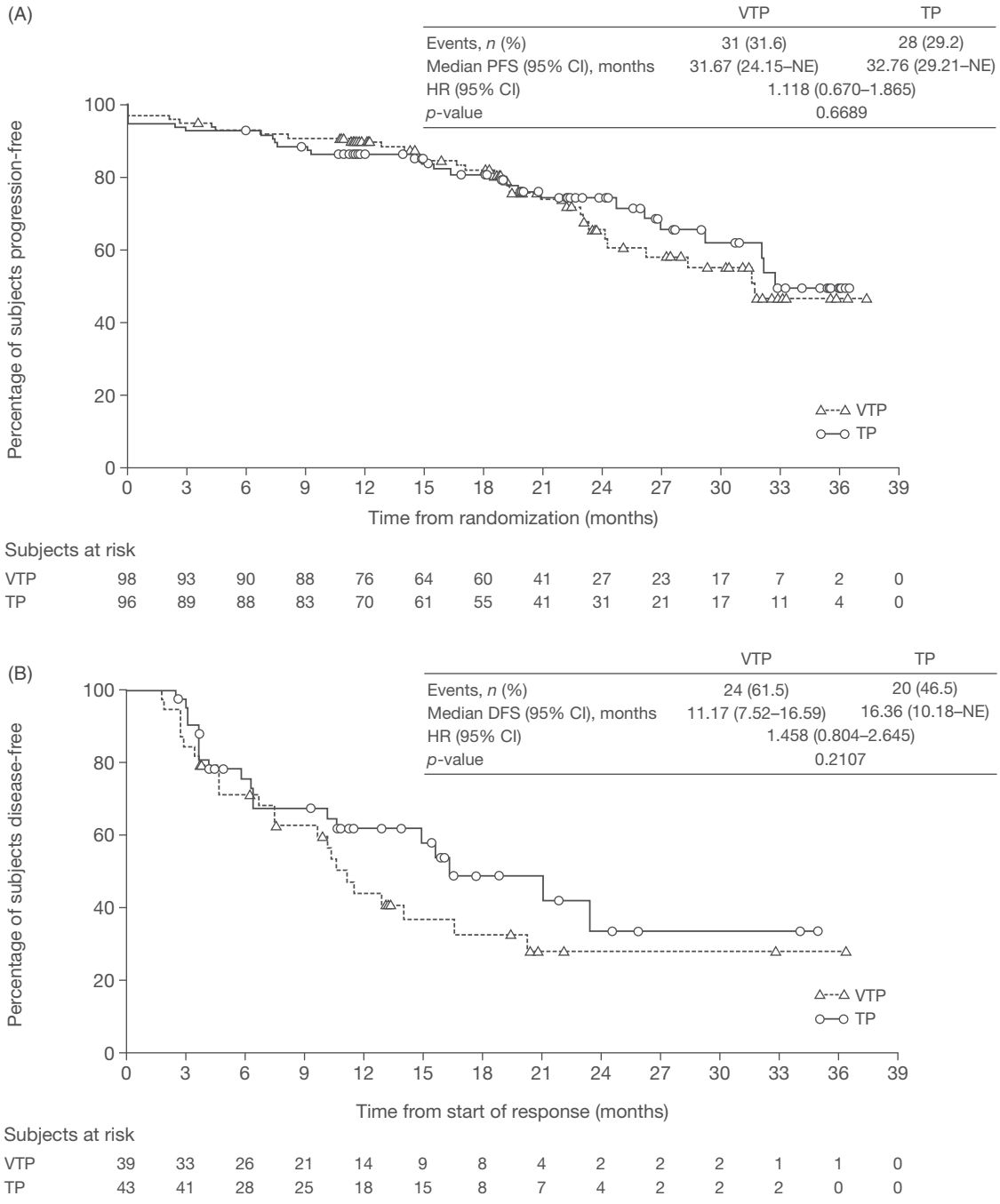

Figure 3. Survival outcomes per computer algorithm: (A) PFS and (B) DFS. CI: confidence interval; HR: hazard ratio; NE: not evaluable; PFS: progression-free survival; TP: thalidomide-prednisolone; VTP: bortezomib-thalidomide-prednisolone.

median prednisolone treatment duration was 10.2 months (0–13.2) in the VTP arm and 10.2 months (0–13.8) in the TP arm.

During consolidation, 96% and 99% of patients in the VTP and TP arms, respectively, reported a TEAE of any grade (Table 4); drug-related TEAEs occurred in 87% ($n = 90$) and 91% ($n = 90$) of patients, respectively. Most frequent all-cause TEAEs were PN (62%) and upper respiratory tract infection (38%) in the VTP arm, and PN (63%) and constipation (38%) in the TP arm. In total, 28% and 36% of patients in the VTP and TP arms had grade $\geq$3 TEAEs (Table 4). The most frequent were pneumonia (5%) and neutropenia (4%) in the VTP arm, and PN (8%) and pneumonia (6%) in the TP arm. The frequency of PN (all grades) during consolidation was 62% ($n = 64$) in the VTP arm and 63% ($n = 62$) in the TP arm; most events were grade 1 or 2, grade $\geq$3 PN occurred in 2% in the VTP arm and 8%

Table 4. Most frequent all-cause TEAEs of any grade (occurring in ≥10% of patients in either arm) and grade ≥3 (in ≥2% of patients in either arm) during consolidation.

TEAE, *n* (%)	VCD induction (*n* = 254)	VTP (*n* = 103)	TP (*n* = 99)
Any TEAE	245 (96.5)	99 (96.1)	98 (99.0)
Peripheral neuropathy NEC[a]	98 (38.6)	64 (62.1)	62 (62.6)
Upper respiratory infection	30 (11.8)	39 (37.9)	32 (32.3)
Constipation	92 (36.2)	29 (28.2)	38 (38.4)
Weight increased	7 (2.8)	17 (16.5)	26 (26.3)
Insomnia	56 (22.0)	13 (12.6)	22 (22.2)
Diarrhea	32 (12.6)	16 (15.5)	15 (15.2)
Peripheral edema	44 (17.3)	16 (15.5)	15 (15.2)
Fatigue	61 (24.0)	16 (15.5)	18 (18.2)
Neuralgia	19 (7.5)	16 (15.5)	15 (15.2)
Cough	14 (5.5)	15 (14.6)	8 (8.1)
Back pain	27 (10.6)	12 (11.7)	10 (10.1)
Nausea	82 (32.3)	12 (11.7)	10 (10.1)
Tremor	12 (4.7)	11 (10.7)	11 (11.1)
Muscle spasm	6 (2.4)	11 (10.7)	9 (9.1)
Herpes zoster	8 (3.1)	7 (6.8)	11 (11.1)
Any grade ≥3 TEAE	93 (36.6)	29 (28.2)	36 (36.4)
Pneumonia	6 (2.4)	5 (4.9)	6 (6.1)
Neutropenia	15 (5.9)	5 (4.9)	0
Peripheral neuropathy	6 (2.4)	2 (1.9)	5 (5.1)
Herpes zoster	1 (0.4)	1 (1.0)	2 (2.0)
Respiratory tract infection	1 (0.4)	1 (1.0)	2 (2.0)
Peripheral sensory neuropathy	3 (1.2)	0	3 (3.0)
Thrombocytopenia	1 (0.4)	0	2 (2.0)

Data reported for the all-treated-randomized analysis set. NEC: not elsewhere classified; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TP: thalidomide-prednisolone; VCD: bortezomib-cyclophosphamide-dexamethasone; VTP: bortezomib-thalidomide-prednisolone.
[a]Medical Dictionary for Regulatory Activities (MedDRA) system organ class.

in the TP arm. Overall, the incidence of hematologic TEAEs during consolidation was low (VTP versus TP, anemia: 3% versus 1%; leukopenia 0% versus 1%; neutropenia 5% versus 0%; pancytopenia 0% versus 1%; thrombocytopenia 2% versus 3%).

Serious adverse events (SAEs) were experienced by 28 patients (27%) in the VTP arm and 22 patients (22%) in the TP arm; drug-related SAEs were reported in 15 (15%) and eight patients (8%). In the VTP and TP arms, respectively, 14 (14%) and eight (8%) patients discontinued treatment due to drug-related TEAEs. Overall, 85 patients discontinued the study; 53 discontinuations occurred prior to randomization and 32 post-randomization (VTP: 18; TP: 14). The most common reasons for discontinuation before randomization were TEAEs and physician's decision ($n = 14$ [5%] each). The most common reason for discontinuation post-randomization in both treatment groups was TEAEs (VTP: $n = 13$ [13%]; TP: $n = 8$ [8%]) and PD (VTP: $n = 5$ [5%]; TP: $n = 6$ [6%]). Reasons for discontinuation pre-randomization are summarized in Supplemental Table 1. There were no deaths due to drug-related TEAEs during consolidation in either treatment group.

Health-related quality of life

Mean scores assessed by the Assessment of Quality of Life-6 Dimensions questionnaire at the end of consolidation therapy were largely similar between the two treatment arms. In general, minimal changes in HRQoL were observed versus baseline, with slight improvements in independent living, relationships, and coping, and a slight increase in pain scores (data not shown).

Results of patient-reported symptoms of PN assessed by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group (FACT/GOG-Ntx) questionnaire were similar between treatment groups. The mean change from baseline in FACT/GOG-Ntx total score, trial outcome index, and FACT/GOG total score was maintained throughout the consolidation phase of the study (data not shown).

Discussion

This phase 3 study was designed to build upon the Australasian Leukemia and Lymphoma Group (ALLG) MM6 study of post-ASCT consolidation with thalidomide and alternate day prednisolone in MM [17]. The study was designed to assess the ability of the addition of bortezomib to standard TP consolidation to deepen the responses and improve the outcomes in patients with NDMM, following three cycles of VCD induction (utilizing SC bortezomib) and ASCT. The percentage of patients achieving ≥ VGPR improved during consolidation treatment in both treatment arms. VTP resulted in

Table 5. Patient response pre- and post-bortezomib-based consolidation in previous studies.

Treatment agent/ combination	Duration of treatment	Regimen	Median follow-up (months)	≥VGPR before consolidation (%)	≥VGPR following consolidation (%)	Reference
Bortezomib (phase 3 trial) $n = 187$	Two 21 day cycles + four 28-day cycles	Two 21-day cycles: bortezomib 1.3 mg/m^2 twice weekly, days 1, 4, 8, and 11. Four 28-day cycles: bortezomib 1.3 mg/m^2 once weekly, days 1, 8 and 15	38	39.7	70.9	[13]
VTD (phase 3 trial) $n = 160$	Two 35-day cycles (following double ASCT)	Bortezomib 1.3 mg/m^2, days 1, 8, 15, and 22; thalidomide 100 mg daily; dexamethasone 40 mg, days 1, 2, 8, 9, 15, 16, 22, and 23	30.4 (from start of consolidation)	86.2	91.9	[15]
VTD (retrospective study) $n = 121$	Two 21-day cycles	Bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11; thalidomide 100 mg/d; dexamethasone 40 mg weekly	30	76	83	[30]
VRD (phase 2 trial) $n = 31$	Two 21-day cycles	Bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11; lenalidomide 25 mg per day, days 1–14; dexamethasone 40 mg weekly	39	70	87	[31]
PAD (phase 3 trial) $n = 413$	Three 28-day cycles	Bortezomib 1.3 mg/m^2 per day on days 1, 4, 8, and 11; doxorubicin 9 mg/m^2 per day on days 1–4, and oral dexamethasone 40 mg per day on days 1–4, 9–12, and 17–20	41	62[a]	76	[26]

ASCT: autologous stem cell transplantation; PAD: bortezomib-doxorubicin-dexamethasone; VGPR: very good partial response; VRD: bortezomib-lenalidomide-dexamethasone; VTD: bortezomib-thalidomide-dexamethasone.
[a]≥VGPR following induction before ASCT and consolidation.

a trend for improvement in the ≥ VGPR rate after 12 months compared with TP; however, statistical significance was not reached (85.7% versus 77.1%; rate difference 8.6%; 95% CI −2.3% to 19.5%; $p = .122$). Additionally, there were no statistically significant differences in the secondary endpoints of PFS, DFS, and HRQoL between arms. Indeed, DFS rates were numerically lower with VTP versus TP, although the number of events at date of cutoff is insufficient to draw robust conclusions for the secondary and exploratory endpoints. Both VTP and TP were well tolerated by patients with no new or unexpected safety concerns, demonstrating the feasibility of adding 16 doses of SC bortezomib to TP in patients who received ASCT after bortezomib-based induction therapy, albeit without significantly improving efficacy outcomes.

The study was limited by slow patient accrual, which resulted in lower-than-planned-target randomization (100 patients per arm; original planned randomization: 120 patients per arm) and therefore reduced the overall power to detect a statistically significant difference in the primary endpoint from 80% to 72%. Additionally, only 79% (200/256) of enrolled patients were randomized; discontinuation pre-randomization was most commonly due to TEAEs (5.5%), physician decision (5.5%), and PD (3.1%).

The utility of bortezomib as consolidation therapy in NDMM has been demonstrated in previous studies. In a phase 3 Nordic Myeloma Study Group trial, single-agent bortezomib consolidation was shown to be active and to increase depth of response [13]. Additionally, an Italian study reported superior response improvements with VTD consolidation (post-VTD induction) compared with TD consolidation (post-TD induction) [15]. Notably in the current study, in contrast with the majority of prior studies [13,15,18], patients in both treatment arms had already received proteasome inhibitor-based induction (VCD, the induction regimen found to be effective and tolerable in the DSMM XI trial [19]), and none had been exposed to an IMiD during induction. Consequently, both treatment arms were IMiD-naive but bortezomib-exposed when starting consolidation therapy, so it is possible that subsequent efficacy improvements were driven by new exposure to the IMiD thalidomide, and were therefore similar in both arms; thus, the hypothesized improvement of 15% was not achieved, leading to the lack of statistical significance. The benefit of additional proteasome inhibitor

consolidation in addition to a class switch to IMiD for deepening response may be limited.

Although our study was not designed or statistically powered to detect significant differences in ≥VGPR rates in patient subgroups, it is notable that in a subgroup analysis the percentage of patients achieving ≥VGPR was numerically higher with VTP versus TP in patients with high-risk cytogenetics. Consistent with these data, previous studies have indicated that thalidomide-based regimens (not containing a proteasome inhibitor) during induction or maintenance may be suboptimal for patients with high-risk cytogenetics [20–22], and proteasome inhibitor-IMiD-steroid combination therapies are recommended for these patients, albeit in a different setting [23].

The current study employed a 3-cycle induction period, in line with current practice guidelines in Australia, which recommend 3–6 cycles of induction [11]. A study by Moreau et al. demonstrated a ≥VGPR rate of 56.2% (ORR = 83.4%) following induction with four cycles of SC VCD, which is a considerably higher VGPR rate than in the current study and may be due to the greater number of induction cycles received by patients or the greater dose of dexamethasone received per cycle (320 mg versus 160 mg in the current study) [24]. Similarly, induction with four cycles of VCD including 320 mg dexamethasone per cycle demonstrated a 61% ≥VGPR rate pre-ASCT in a population of patients with NDMM [25], which supports the potential response benefit with increased dexamethasone dose. Three induction cycles have been used in other studies in MM, including with PAD and VTD regimens, with no detrimental effect on post-HDT/ASCT response rates [15,26], so it is unclear whether the number of cycles contributed to the lower ORR and ≥VGPR rates observed in this study. It is also possible that the SC route of administration of bortezomib influenced the post-induction and post-HDT/ASCT response rate (Table 5) [27,28].

In other studies involving bortezomib-based consolidation regimens, bortezomib treatment duration was similar to our study. For example, the previously mentioned study by Cavo et al. involved two 35-d cycles of VTD consolidation treatment, with 1.3 mg/m^2 bortezomib administered on days 1, 8, 15, and 22 of each cycle, and resulted in significant response improvements with VTD versus TD [15]. It is possible that the fortnightly bortezomib dosing schedule in the current study was not sufficiently dose-intensive to result in efficacy improvements. However, in a non-transplant study of bortezomib-melphalan-prednisone, a fortnightly bortezomib schedule as maintenance therapy resulted in an increased response rate [29], suggesting that this dose intensity is sufficient to see response benefits.

It should also be noted that the distribution of patients across Australia, Korea, and China was not equal. Most patients were white (79%), 23% were Asian, 2% were of other races, and 4% were of unknown race or not reported. Therefore, the results presented here may not be representative of the efficacy and safety of bortezomib-based consolidation following ASCT in all NDMM patients.

In the current study, the addition of 32 weeks of bortezomib to TP consolidation was associated with limited additional toxicity with similar rates of drug-related TEAEs reported in each treatment group; however, the rate of discontinuation due to TEAEs was higher with VTP versus TP treatment. The rate of all-cause, any-grade PN was more than 60% in both treatment groups, but it was mostly grade 1 or 2 and was similar with VTP and TP. Indeed, the rate of grade 3 PN was higher with TP than VTP, indicating that bortezomib did not impact PN rates. Furthermore, during induction, the PN rate was low (38.6%) and events were primarily low-grade (3.5% grade ≥3). Hematologic toxicities were reported infrequently in the current study and their incidences were similar in the VTP and TP treatment groups. Both VTP and TP were well tolerated as consolidation therapy by the majority of patients. Although the use of thalidomide in frontline therapy has largely been superseded by newer, novel drugs for NDMM in nations with a large healthcare budget, in the region in which this study was conducted TP remains an important regimen. For many patients globally, the more recent therapies for MM are inaccessible and/or unaffordable and TP continues to be widely used [9,10].

Conclusion

The results presented here demonstrate that the VTP triplet combination is feasible as consolidation therapy in NDMM patients following VCD induction therapy and ASCT. VTP in this clinical context has acceptable tolerability. However, the improvement in the ≥VGPR rate after 12 months in comparison to TP was not statistically significant, and secondary efficacy outcomes were similar between arms. Based on these findings, addition of bortezomib to TP resulted in only limited benefit and is not recommended versus TP alone for the overall population of patients with NDMM who have received VCD induction therapy and ASCT. ClinicalTrials.gov identifier: NCT01539083.

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Potential conflict of interest:

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