Safety and efficacy of vorinostat, bortezomib, doxorubicin and dexamethasone in a phase I/II study for relapsed or refractory multiple myeloma (VERUMM study: vorinostat in elderly, relapsed and unfit multiple myeloma)

Over the last decade, novel agents (NA) have substantially improved the survival of multiple myeloma (MM) patients. However, long-term treatment efficacy and tolerability remain crucial challenges in the management of relapsed and refractory (RR) MM (RRMM).[1] Those patients refractory to NA, including proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), have a poor median progression-free survival (PFS) and overall survival (OS).[2] Only 20% of such patients achieve responses on subsequent bortezomib-containing regimens, highlighting an urgent need for novel regimens that may recapture responses in PI- and IMiD-refractory patients (*clinicaltrials.gov Identifier: 01394354*).

Histone deacetylases (HDACs) are enzymes that play a key role in regulating gene expression and in controlling cellular activities in multiple pathways involved in cancer cell growth. Different HDACs have been reported: class I, IIA, IIB, III, and IV. Due to their effect on posttranslational modifications, HDACs activate vascular endothelial growth factor and Akt pathway signaling, both crucial drivers of plasma cell (PC) propagation. Albeit HDAC inhibitors (HDACi) alone displayed limited single agent antimyeloma activity, combinations gained worldwide interest.[3-5] In MM, PC differentiation and survival depend on the activation of unfolded protein response, which results in upregulation of protein degradation by the 26S proteasome. HDAC6, a member of the IIB histone deacetylase subclass, mediates trafficking of ubiquitinat-

Table 1A. Review of literature using different HDACi in multiple myeloma patients.

#	Trial	HDACi schedule	∑ HDACi dose (mg)	# Prior lines	n	Phase	Median age (years)	Prior PI, IMiD, SCT (%)	Response	Reference
1	VERUMM (VBDD)	VOR 100-300mg d1-4,8-11,15-18 (4-wk cycle)	1200-3600	3 (range 1-9)	33	I/II	62 (47-77)	88, 42, 91	ORR 67% PFS 9.6 months OS 33.8 months	Waldschmidt *et al.* (2018)
2	VB-pegDox	VOR 400mg d4-11 (3-wk cycle)	3200	2 (range 1-9)	32	32 I	61 (39-75)	78, 91, 66	ORR 65% PFS 13.9 months	Voorhees *et al.* (2017)
3	VANTAGE 095 (VOR-V)	VOR 400mg d1-14 (3-wk cycle)	5600	4 (range 2-17)	142	IIb	63 (37-81)	n.g.	ORR 11% PFS 7 months OS 11.2 months	Siegel *et al.* (2016)
4	VANTAGE 088 (VOR-V *vs.* V)	VOR 400mg d1-14 (3-wk cycle)	5600	1-3 (excluding V resistance)	637	III	61 (30-85)	25, 61, n.g.	ORR 56% *vs.* 40.6% PFS 7.6 *vs.* 6.8 months OS nr *vs.* 14 months	Dimopoulos *et al.* (2013)
5	VOR-RD	VOR 400mg d1-7 + d15-21	5600	5 (median, LEN refractory)	25	IIb	65 (48-82)	80, 36, 96	ORR 24% PFS 5.3 months	Sanchez *et al.* (2017)
6	VOR-V	VOR 200-400mg d1-14, bid/qd	5600-8400	4 range (1-14)	34	I	61 (45-79)	53, 56, 53	ORR 33%	Weber *et al.* (2012)
7	VOR-V	VOR 100-500mg d1-8 (3-wk cycle)	800-4000	7 (range 3-13)	23	I	54 (39-78)	83, 74, 87	ORR 42%	Badros *et al.* (2009)
8	PANORAMA-2 (PAN-VD)	PAN 20mg d1,3,5,8,10,12: 6-wk cycles, 2/1 wks on/off	120	4 (median)	55	II	61 (41-88)	100, 98, 56	ORR 55% PFS 6 months OS 9 months	Richardson *et al.* (2016)
9	PANORAMA-1 (PAN-VD *vs.* VD)	PAN 20mg d1,3,5,8, 10,12: 6-wk cycles, 2/1 wk on/off	120	2 (range 1-3)	768	III	63 (56-69)	44, 19, 56	ORR 61% *vs.* 51% PFS 12 *vs.* 8 months OS 34 *vs.* 30 months	San Miguel *et al.* (2014)
10	RIC RIC-VD	RIC 160mg d1-5, d8-12, 3-wk cycle)	1600	4 (range 2-11) 5 (range 2-12)	15 57	I II	70 (51-79)	100, n.g., n.g.	ORR (RIC) 0% PFS/OS not reached ORR (RIC-VD) 37%	Vogl *et al.* (2017)
11	RIC-RD	RIC 40-240mg 2x/d; d1-21, 4-wk cycle)	840-5040	2 (range 1-3)	38	Ib	63 (57-71)	84, 68, 50	ORR 55% PFS 20.7 months OS not reached	Yee *et al.* (2016)

VBDD: vorinostat-bortezomib-doxorubicine-dexamethasone; VOR-V: vorinostat-bortezomib; V: bortezomib; Vor-RD: vorinostat-lenalidomide-dexamethasone; Pan-VD: panobinostat-bortezomib-dexamethasone; qd: once daily; bid: twice daily; RIC: ricolinostat; RIC-VD: ricolinostat-bortezomib-dexamethasone; RIC-RD: Ricolinostat-lenalidomide-dexamethasone; wk: week; nr: not reached; d: day; ORR: overall response rate, PFS: progression-free survival, OS: overall survival; PI: proteasome inhibitors; IMiD: immunomodulatory drugs; SCT: stem cell transplantation; HDACi: histone deacetylases inhibitor; LEN: lenalidomide.

Table 1B. Patient demographics, baseline characteristics and disease history.

Variables	n (%)	Median (range)
Number of patients	33	
Age (years)		62 (47-77)
Sex (m : f)	19 (58%) : 14 (42%)	
Karnofsky performance status (KPS; %)		90 (70-100)
Type of myeloma		
IgG/IgA / Light chain only myeloma	17 (52%) / 11 (33%) / 5 (15%)	
Light chain κ *vs.* λ	20 (61%) / 13 (39%)	
Durie & Salmon stage		
I / II / III	1 (3%) / 2 (6%) / 30 (91%)	
A / B	29 (88%) / 4 (12%)	
ISS stage		
I *vs.* II / III	4 (13%) / 28 (87%)	
Bone marrow infiltration rate (%)		40 (6-90)
Cytogenetics (CG *via* iFISH)[a]		
High-risk[a1]	6 (18%)	
Unfavorable[a2] : favorable[a3] CG	17 (52%) : 16 (48%)	
Prior therapies		3 (1-9)
SCT	30 (91%)	
Bortezomib	29 (88%)	
IMiDs	14 (42%)	
Myeloma status at baseline		
Relapsed[b]	23 (70%)	
Relapsed and refractory[b]	10 (30%)	

[a1]High-risk cytogenetics: t(4;14), del 17p.[a2]Definition of unfavorable CG: del(17p13), t(4;14), t(14;16); t(14;20), c-myc overexpression/translocation and chromosome 1 aberrations.[a3]Favorable CG: t(11;14), hyperdiploidy, isolated del13q14, normal karyotype. [b]Definition of relapsed/refractory multiple myeloma. Relapsed multiple myeloma: previously treated myeloma that progresses, and requires initiation of salvage therapy >60 days after last therapy. Relapsed and refractory multiple myeloma: nonresponsive while on salvage therapy or PD within 60 days of last therapy after ≥ minimal response (MR). κ/λ: kappa/lambda light chain, iFISH: interphase fluorescence *in situ* hybridization; SCT: autologous stem cell transplantation; IMiDs: immunomodulatory drugs; Ig: immunoglobulin; CG: cytogenetics; ISS: the International Staging System.

ed proteins to the aggresome/autophagy pathway. This second mechanism of protein degradation represents a central alternative for cells exposed to proteasome inhibition, underlining the susceptibility of bortezomib-treated myeloma cells to HDAC6 inhibition. Vorinostat is an oral class I/II HDACi and has been investigated with bortezomib in a randomized phase III trial for RRMM patients: this VANTAGE088 study reported a median PFS of 7.6 *vs.* 6.8 months for vorinostat and bortezomib *vs.* bortezomib-control, and the PANORAMA1 trial noted a median PFS of 12 *vs.* 8 months for panobinostat-bortezomib-dexamethasone (PAN-VD) *vs.* VD-control, respectively.[4,5] This observation led to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval for PAN-VD, but vorinostat remains impeded to date. Aiming for a feasible and potent protocol, our Investigator-Initiated-Trial (IIT) was designed to reassess the therapeutic value of vorinostat in RRMM patients (details in *Online Supplementary Methods*). Based on observations suggesting that the combination of HDACi and doxorubicin potentiates apoptosis in MM,[6] and due to the synergy between vorinostat and bortezomib,[7] our quadruplet vorinostat (V), bortezomib (B), doxorubicin (D), dexamethasone (D; VBDD/VERUMM) was designed (Table 1A). The synergism of vorinostat and bortezomib is depicted in *Online Supplementary Figure S1A.*

All patients suffered from relapse (n=23) or RRMM (n=10). The median age was 62 years, which was comparable or more advanced to others (Table 1A,B). In line with our earlier description of age and stage migration,[8] we here observed more elderly, unfit and advanced MM stages.[8-10] The Revised Myeloma Comorbidity Index (R-MCI) was 4, thus patients were by definition intermediate-fit.[9,10] Furthermore, their Charlson Comorbidity Index (CCI) was 2 *vs.* 1 in our control patients (Table 1C). For comparison, Palumbo *et al.* described their elderly clinical trial cohort with a CCI of 0.[11]

Our pretreatment with PIs, IMiDs and autologous stem cell transplantation (ASCT) was similar to that of others.[5,12,13] The number of prior lines was 3: virtually all (91%) had received ASCT, bortezomib (88%) and IMiDs (42%). The median bone marrow (BM) infiltration was 40%, interphase fluorescence *in situ* hybridization (iFISH) showed high risk (HR) in 18% and unfavorable cytogenetics (CG) in 52% (Table 1A,B). The VBDD data were presented in December 2016 with at least a one year follow-up of the last patient being treated. At that time, NAs, such as daratumumab (Dara), elotuzumab, carfilzomib or ixazomib, had not yet been available for RRMM patients outside clinical trials.[14]

With 3 patients having been treated at dose levels (DL) 0 and +1, without any dose-limiting toxicity (DLT) during the first cycle, the remaining 27 proceeded to DL+2. Common hematologic adverse events (AEs) included anemia and thrombocytopenia. Non-hematologic AEs

Table 1C. Median comorbidity and quality of life indices before and after VBDD treatment (end of treatment [EoT]), and as compared to prospective and entire MM cohorts.

Test	Baseline (BL) (n=33)	EoT (n=27)	Median change from BL (n=27)	*P* change from BL to EoT	Prospective UKF control cohort (n=280)	Entire UKF MM control group (n=1054)
1. Subjective fitness rating						
Fitness rating by physician	3	3	0	0.696	3	–
Fitness rating by patient	3	3	0	0.382	3	–
2. Functional comorbidity tests						
Karnofsky performance status (%)	70	90	10	**<0.001**	80	70
Timed up and go test (sec)	9	9	0	0.813	10	–
Pain	2	1	0	0.130	2	–
IADL	8	8	0	0.813	8	–
Mini Mental State Examination	29	29	0	0.781	28	–
Geriatric Depression Scale	3	2	0	0.404	2	–
Malnutrition	3	3	1	0.225	3	–
3. Functional comorbidity scores						
R-MCI	4	3	-1	**<0.001**	4	5
CCI	2	1	0	**0.0002**	2	1
HCT-CI	1	0	-1	**0.001**	2	2
IMWG-frailty index	1	0	0	**0.002**	1	1
Kaplan Feinstein Index	1	1	0	0.585	1	2
eGFR / β2-MG score	1	1	0	1	1	1

Prospective UKF control cohort (n=280): prospectively assessed MM patients *via* subjective fitness ratings, functional comorbidity tests and functional comorbidity scores, in line with VBDD cohort. Entire UKF MM control group (n=1054): both retrospectively and prospectively assessed MM patients at our center, who were initially assessed *via* KPS and 6 functional comorbidity scores. Pain: 0-10 pain scale; IADL: instrumental activities of daily living; Malnutrition: prideaux nutritional risk assessment. UKF: University Clinic Freiburg; R-MCI: revised myeloma comorbidity index; CCI: charlson comorbidity index; HCT-CI: hematopoietic cell transplantation comorbidity index; sec: seconds; MM: multiple myeloma; IMWG-frailty index: International Myeloma Working Group index; eGFR - ß2-MG score.[9,10]

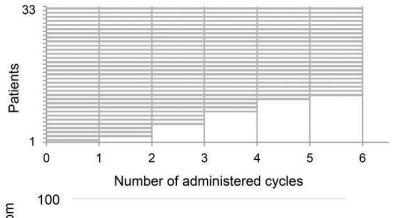
included infections, amongst which there were 3 cases of sepsis, 3 of pneumonia, and 1 each with esophageal candidiasis, colitis and herpes zoster reactivation. Other side effects included 1 case of syncope and cerebral seizure in a patient with seizure history (Table 2). Cardiotoxicity was not observed: median N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were 186pg/ml (norm:<125pg/ml) before and insignificantly different after VBDD with 203pg/ml. In 2/33 patients, a relation to VBDD was suspected: 1 herpes zoster reactivation (despite acyclovir prophylaxis), and 1 bacteremia. Both of these patients recovered after standard care measures. With supportive medication (pantoprazole, cotrimoxazol, acyclovir, granisetron, enoxaparin, pamidronate or zolendronate), VBDD tolerability was favorable as compared to that of BDD.[15]

A total of 33 patients received at least 1 VBDD cycle and most completed 6 scheduled cycles (67%, Figure 1A). Response in relapsed and RRMM patients demonstrated substantial efficacy; nearly all patients showed a decrease in their paraprotein and disease burden. At the end of therapy (EoT), ~2/3 of patients had lower paraprotein or substantially decreased serum free light chain levels than they had prior to VBDD (Figure 1B). The best overall response rate (ORR) was 67%, and remained at 61% at the EoT; the clinical benefit rate (CBR) was 94% and 88%, respectively (Figure 1C). Response with respect to vorinostat revealed a dose-response relationship, with ORRs in DL0, +1 and +2 increasing from 33% to 66% and 70%, respectively (Figure 1C). ORR in CG-subgroups amounted to 50%, 47% and 88% in HR, unfavorable and favorable patients, respectively. Since various groups describe 'unfavorable' CG, albeit not extensively HR, if 1q- and c-myc abnormalities are present, this group combined with that of HR patients was also assessed (Figure 1D).

Of interest, 7 patients had been refractory to bortezomib (relapse on VD, bortezomib-cyclophosphamide-dexamethasone (VCD) or bortezomib-thalidomide-dexamethasone (VTD) in 4, 2 and 1 patient, respectively), whilst 3 were refractory on lenalidomide-dexamethasone (Rd). The response in bortezomib-refractory patients was 3 partial responses (PR), 1 minor response (MR), 2 stable diseases (SD) and 1 progressive disease (PD; this latter being a plasma cell leukemia [PCL]). Rd-refractory patients all showed PR to VBDD. Comparison of our VBDD results to other HDACi trials was favorable, while AEs were effectively manageable (Table 1A).[3,4,12,13,16-21]

Bone marrow plasma cell (BMPC) infiltration rates and immunohistochemistry (IHC)-CD38 and HDAC6 expression were assessed before and during VBDD (*Online Supplementary Figure S3*, Figure 1 E,F). Moreover, we assessed the relative pan-HDAC activity in peripheral blood mononuclear cells (PBMCs) before and during the second VBDD cycle. Decreases in relative HDAC activity in 11/16 patient samples were observed (Figure 1G). As

A



B

C

Best response	Dose level (DL) 0 (n=3)	DL +1 (n=3)	DL +2 (n=3+24=27)	All pts (n=33)
CR / vgPR / PR	- / - / 1	- / - / 2	1 / 7 / 11	1 / 7 / 14
SD / PD	2 / -	1 / -	6 / 2	9 / 2
ORR (≥PR)	1 (33%)	2 (66%)	19 (70%)	22 (67%)
CBR (≥SD)	3 (100%)	3 (100%)	25 (93%)	31 (94%)
End of treatment				
CR / vgPR / PR	- / - / 1	- / - / -	- / 8 / 11	- / 8 / 12
SD / PD	2 / -	3 / -	4 / 4	9 / 4
ORR (≥PR)	1 (33%)	0	19 (70%)	20 (61%)
CBR (≥SD)	3 (100%)	3 (100%)	23 (85%)	29 (88%)

D

Best response in various cytogenetic risk groups

Cytogenetic risks	High risk (HR) t(4;14) (n=1)	High risk (HR) del17p (n=5)	+ 1q + myc abnormalities 1q abnorm (n=6)	+ 1q + myc abnormalities 1q+myc (n=2)	+ 1q + myc abnormalities cmyc (n=3)	HR[1] (n=6)	Unfavorable[2] (n=17)	Favorable[3] (n=16)
CR / vgPR / PR	- / - / 1	- / - / 2	- / 2 / 2	- / - / -	- / - / 1	- / - / 3	- / 2 / 6	1 / 5 / 8
SD / PD	- / -	3 / -	1 / 1	2 / -	1 / 1	3 / -	7 / 2	2 / -
ORR (≥PR)	1 (100%)	2 (40%)	4 (67%)	0	1 (33%)	3 (50%)	8 (47%)	14 (88%)
CBR (≥SD)	1 (100%)	5 (100%)	5 (83%)	2 (100%)	2 (67%)	6 (100%)	15 (88%)	16 (100%)

Abbreviations and definitions:
[1]HR: t(4;14; t(14;16); t(14;20), del17p: n=6; [2]unfavorable: HR + 1q- and cmyc-abnormalities: n=17; [3]favorable: hyperdiploidy; no HR or unfavorable features: n=16

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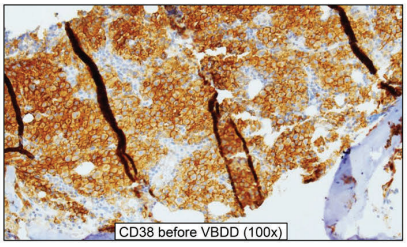

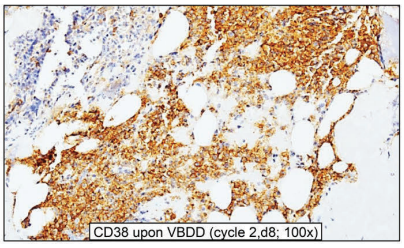

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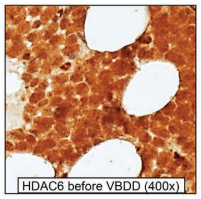

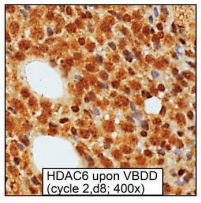

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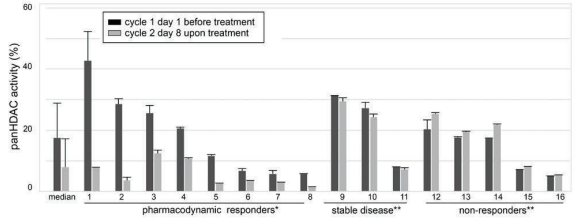

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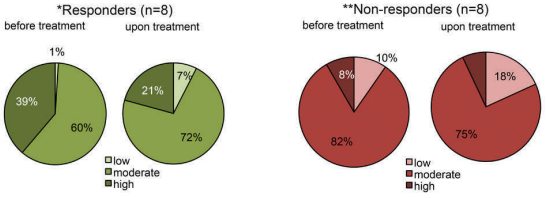

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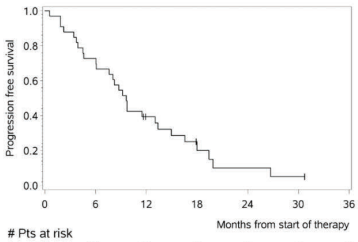

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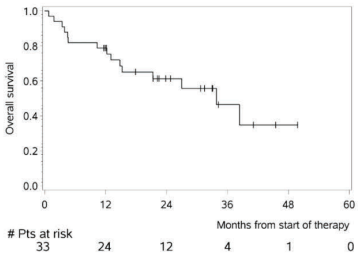

Figure 1. Clinical and biomarker results of VBDD treatment in RRMM patients A. Number of administered cycles of VBDD therapy: 22 of 33 patients received 6 cycles of therapy. Of the remaining 11 patients more than half received at least 3 VBDD cycles. B. Best serologic response. Waterfall plot depicting the best serologic response (Ig, light chain) from baseline in %; response rates of RRMM patients additionally highlighted in black. C. Best response, and at the end of treatment in dose levels 0, +1 and +2 in all 33 MM patients. D. Response in cytogenetic risk groups. ORR to VBDD amounted to 50%, 47% and 94% in cytogenetically HR, unfavorable and favorable patients, respectively. E. IHC of BM sections with CD38$^+$ plasma cell (PC) infiltrates before (left, Giemsa stain, 100x) and upon VBDD treatment (right, Giemsa stain, 100x) depicting a decrease of CD38$^+$ PCs in the BM during treatment. F. IHC was carried out for HDAC6 before (upper panel) and during (lower panel) treatment with a moderate to strong cytoplasmic and nuclear positivity in the PCs. (Giemsa, 400x); of note is the decreasing intensity of HDAC6 positivity over the course of time (and treatment). G. Pan-HDAC activity in PBMCs (evaluated by enzyme assay). VBDD treatment led to substantial downregulation of HDAC activity in the PBMCs of responding patients (11/16 patients [69%]) with median HDAC activity decreasing to 45% as compared to pre-treatment levels (P=0.113). H. Responders in terms of diminished PBMCs' HDAC activity exhibited considerably higher HDAC6 expression levels at VBDD therapy initiation within the BM, which seemed associated with favorable treatment response, and could possibly serve as a marker for rational HDACi treatment. Parallel to the downregulation of HDAC activity in PBMCs, BM HDAC6 expression decreased during therapy, whereas in non-responders it remained almost unaffected. I,J. Kaplan-Meier estimates of PFS (I) and OS (J). ORR: overall response rate; MM: multiple myeloma; CR: complete response; vgPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; CBR: clinical benefit rate; VBDD: vorinostat-bortezomib-doxorubicin-dexamethasone; d: day.

early as on day 8 of cycle 2, the median HDAC activity decreased to 45% of pre-treatment levels (P=0.113). Responders (≥PR) showed >40% early pan-HDAC activity decreases in PBMCs, whereas pan-HDAC activity remained either unchanged, modestly decreased or increased in patients with SD or no response (Figure 1G).

Based on PBMC-HDAC decline (decrease of PBMC-HDAC activity from VBDD initiation to cycle 2, day 8 with a cut-off of ≥15% *vs.* <15%; Figure 1 G,H), patients were classified in pharmacodynamic responders *vs.* SD/non-responders. While both cohorts exhibited similar characteristics regarding age, sex and staging according to the International Staging System (ISS), pharmacodynamic responders had better renal function, CG and lower BMPCs (CD38), associated with improved response to VBDD (*Online Supplementary Table S1*). In line, BMPCs and BM-HDAC6-IHC-expression (Figure 1 E-H) decreased in pharmacodynamic responders during therapy, whilst in nonresponders both remained almost unaffected.

With a median follow-up of 30.8 months, median PFS and OS were 9.6 and 33.8 months, respectively (Figure1 I,J). Maintenance with VD or VTD was performed in 8 and 4 patients, respectively. This may have influenced PFS, however, we considered it important to report PFS as time from start of treatment until PD or death for our entire cohort in order to maintain comparability to other published results, without censoring for start of maintenance or exclusion of patients.

As a subsequent consolidation, ASCT or allogeneic-SCT were performed in 10 and 5 patients, respectively, all of whom had improved their quality of life (QoL) parameters under VBDD. Next-line treatment with pomalidomide/dexamethasone and MOR03087 (anti-CD38ab)/dexamethasone was performed in 1 patient each (*Online Supplementary Figure S2*). Although the response to VBDD was rewarding (Figure 1A-F), progression on VBDD evolved in 4 patients with primary refractory myeloma: all presented with extensively pretreated, extramedullary disease, including 1 with PCL. Two underwent salvage ASCT, but developed neutropenic sepsis and died due to refractory myeloma. Fifteen patients died during subsequent follow-up, all as a consequence of eventually refractory MM. None of these deaths were judged VBDD related.

Before and after VBDD, patients were functionally assessed: Karnofsky Performance Scale (KPS), pain, geriatric depression scale and functional comorbidity scores, such as the revised myeloma comorbidity index (R-MCI), CCI, hematopoietic cell transplantation comorbidity index (HCT-CI), and the International Myeloma Working Group (IMWG)-frailty index improved in responding patients, thus demonstrating the feasibility of the protocol and the lack of physical decline, despite the use of a quadruplet. Median changes from baseline were assessed to adjust for different patient numbers at baseline (n=33) and EoT (n=27; Table 1C). Fitness tests of a prospective cohort and an even larger control group with 280 and 1054 MM patients from our center, respectively, demonstrated that our VBDD patients were representative in baseline comorbidity and QoL, albeit their KPS, depression scale and CCI were compromised as compared to both controls. This suggested that the VBDD cohort consisted of 'real-world' patients, who -due to their relapse- were more compromised in some functional domains than our controls.[9,10]

Despite substantial improvements in the therapeutic landscape for MM during the past years, almost all patients gradually become refractory to currently available treatment options. Patients, relapsed or refractory to bortezomib and lenalidomide, face a grim prognosis, illustrated by an OS of approximately 9-15.2 months.[2] This subgroup of challenging patients drives an unmet need for efficient and tolerable treatment options. Recently, several immunological agents have been approved or are under intensive investigation, leading to new therapeutic options, however, these were unavailable during the course of our VERUMM trial. Current advances are rapid and highly promising, especially in the field of immunotherapies (IO), including monoclonal antibodies or chimeric antigen receptor T (CAR-T) cells. However, since not all patients may profit from IO, and relapse remains inescapable, a better understanding of resistance continues to be a crucial research interest and novel treatment strategies for RRMM are needed.[14,22]

Results from this phase I/II VBDD/VERUMM trial demonstrated encouraging efficacy and tolerability. Due to the favorable responses in previously treated and untreated MM patients with renal impairment (RI) and due to the synergy of vorinostat and the BDD-backbone, this was chosen for our quadruplet.[15] Since various relapse options are available in MM today,[14] doxorubicin is admittedly less frequently used, albeit BDD remains efficient in advanced MM, induces prompt responses and was well-tolerated along with our doses and schedule.[15] To our knowledge, this study is the first to define a vorinostat-based quadruplet, which was administered in the outpatient setting with excellent tolerability. The number of prior lines was substantially higher, as previously observed for the VANTAGE088 trial, with a median of 3 and prior bortezomib treatment in 88%. The ORR and CBR amounted to 67% and 94%, respectively, and with a median follow-up of 30.8 months the median PFS and OS were 9.6 and 33.8 months, respectively. Vorinostat could be successfully increased to 300mg/d; a

Table 2. Adverse events of grade 3/4 (regardless of relationship to study treatment).

	Grade 3	Grade 4
Hematologic		
Anemia	8 (24%)	1 (3%)
Thrombocytopenia	4 (12%)	4 (12%)
Leukopenia / neutropenia	1 (3%) / 1 (3%)	0 / 1 (3%)
Non-hematologic		
Sepsis	3 (9%)	0
Infections*	6 (18%)	0
SIRS	1 (3%)	0
Fatigue	1 (3%)	0
Epistaxis / hematoma	1 (3%) / 1 (3%)	0 / 0
Syncope	1 (3%)	0
Seizure	1 (3%)	0
Limb / spinal cord injury	1 (3%) / 1 (3%)	0
Increased C-reactive protein	2 (6%)	0
Pathologic fracture / osteolysis	1 (3%) / 1 (3%)	0
Vomiting	1 (3%)	0
Increased appetite	1 (3%)	0
Total no of AEs	37	6
No of patients with at least 1 AE	19 (58%)	6 (18%)

*Infections: esophageal candidiasis (n=1), clostridium difficile colitis (n=1), herpes zoster (n=1), and pneumonia/respiratory tract infection (n=3). SIRS: systemic inflammatory response syndrome, no: number, AE: adverse event.

maximum tolerated dose (MTD) was not reached. Subgroup analyses with respect to dose levels revealed deeper responses in patients who received higher vorinostat doses, and encouraging ORRs of 50% and 47%, respectively, were achieved, despite unfavorable and HR CG. AEs were rare and in line with the safety profile of the BDD-backbone, suggesting no addition of toxicity due to HDACi co-treatment.

In previous studies, pan-HDACis have led to cardiac toxicity including cases of arrhythmia and QTC prolongation:[3,13,19] vorinostat doses of 400mg have been associated with a 35% occurrence of cardiac serious adverse events (SAEs), using a different schedule as compared to ours.[16] The previously reported side effects in major vorinostat trials[4,17] might have limited the exposure and efficacy of vorinostat, impeding FDA/EMA approval as opposed to that of panobinostat. Despite our quadruplet, we did not observe more than one grade 3 AE potentially associated with cardiac arrhythmia. This suggests cardiac safety for 300mg within our 4 day on and 4 day off schedule, as compared to previous 'MTD-driven' HDACi trials.[4,16,17] In agreement, our median pro-BNP levels did not change pre- and post-VBDD. Most importantly, our observations indicated that vorinostat can be safely combined with BDD without increased organ toxicity, namely cardiac, renal impairment (RI) or peripheral neuropathy. Considering that the enrolled patients had exhausted various therapies available during study inclusion and suffered from RRMM in 30% of all cases, the combination of oral vorinostat and subcutaneous bortezomib suggested a method of overcoming chemoresistance to bortezomib. VBDD efficacy may be correlating with reappearing clones sensitive to bortezomib.[23] The absence of a statistically significant ORR difference between patients whose last line of therapy prior to VBDD was a bortezomib-containing *vs.* bortezomib-free regimen suggested that the observed efficacy may however be due to vorinostat. QoL assessment under VBDD improved and was associated with response.[10]

Albeit cross-comparison of different trials[15,24] is cumbersome, due to different patients being included and time bias: Palumbo described an ORR with BDD in 67%, a 1-year event-free survival of 34% and a 1-year OS of 66%.[24] Ludwig demonstrated hematologic and renal response to BDD in light chain-induced RI in 18 previously treated and 50 untreated patients:[15] a response was obtained in 72%, the median PFS was 12.1 months, and the 1- and 2-year OS were 72% and 58%, respectively. Our results, all in intensively pretreated RRMM patients, compared very favorably, albeit we cannot entirely prove the additional efficacy of vorinostat to BDD, except in those 7 bortezomib-refractory patients who again responded to VBDD. The efficacy of our VERUMM trial data as compared to both the PANORAMA 1 and 2 trials showed similar ORRs (67% *vs.* 55-61%), PFS (9.6 *vs.* 6-12 months) and OS (33.8 *vs.* 9-34 months, respectively). For exact comparability, Table 1A summarizes all results. Recapturing the complexity of HDAC biology, encouraging progress has been made by the introduction of HDAC6i with low class I HDAC selectivity. Two, ricolinostat and ACY-241, are currently being tested in clinical trials to optimize HDACi combinations.[20,21]

Within the armamentarium for RRMM, our HDACi-quadruplet seems to also be a cost-effective treatment option: we have calculated therapy costs at our center of VBDD *vs.* daratumumab-lenalidomide-dexamethasone (Dara-Rd) or Daratumumab-bortezomib-dexamethasone (Dara-VD), which are 5- and 4-fold higher, respectively. Moreover, our data re-assessed the role of HDACi as a well-tolerated and active option in patients treated as outpatients, without compromising their QoL. Due to its promising efficacy, VBDD may serve as a bridging therapy. Most importantly, our quadruplet may provide useful guidance for other HDACi combinations, demonstrating that it is relevant to successfully employ a continuous epigenetic treatment with proven synergy to others, before HDACi are dismissed as antimyeloma agents. Our findings are also relevant for IO approaches,[22] since all-trans retinoic acid (ATRA) and HDACi have been shown to upregulate CD38 expression, and may thereby induce longer, ongoing responses to IO approaches,[25,26] such as Dara-therapy. We have recently proposed a phase I/II trial which will address this observation and have discussed this IIT with the European Myeloma Network (EMN)/IMWG experts. Further clinical trials are needed in order to define the value of selective HDACis as useful additions to the currently available treatment choices in MM.

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