**Phase 1 Trial Evaluating Vorinostat Plus Bortezomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma**

# A Phase I Trial Evaluating Vorinostat plus Bortezomib, Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma

**Running title:** Vorinostat-VRD for Newly Diagnosed Myeloma

Jonathan L. Kaufman[1*], Roberto Mina[1*], Jatin J. Shah[2], Jacob P. Laubach[3], Ajay K. Nooka[1], Colleen Lewis[1], Charise Gleason[1], Cathy Sharp[1], R. Donald Harvey[1], Leonard T. Heffner[1], Paul Richardson[3], Sagar Lonial[1], and Robert Z. Orlowski[4]

**JLK and RM equally contributed to the manuscript and share the first authorship*.

[1] Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, US-GA.
[2] Currently employed by Karyopharm Therapeutics, Newton, US-MA.
[3]LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Research, Harvard Medical School, Dana-Farber Cancer Institute, Boston, US-MA.
[4]Department of Lymphoma/Myeloma, The University of Texas, MD Anderson Cancer Center, Houston, US-TX

**Corresponding Author:** Dr. Roberto Mina, MD, Hematology and Medical Oncology, Winship Cancer Institute, Emory University, 1365C Clifton Rd, Atlanta, GA 30322, USA. +1 778-4322 Email: roberto.mina.rm@gmail.com

**Conflict of interest disclosures**
J.L.K. has consulted for Roche, AbbVie, Janssen, BMS, Takeda and Karyopharm. R.M. has received honoraria from Amgen, Celgene, Takeda and Janssen and served on the advisory boards for Janssen. J.J.S. is currently employed by Karyopharm Therapeutics, Newton, US-MA. J.P.L. has received research funding from Novartis, Onyx, Celgene and Millennium. L. T. H. has received honoraria from Pharmacyclics and institutional research funding from Pharmacyclics and Genentech. R.D.H. has received research funding from Amgen and Novartis. A.K.N. has served on the advisory board for GSK, Spectrum, Celgene, Amgen, Novartis Pharmaceuticals, Adaptive Biotechnologies; has received honoraria from Bristol-Myers Squibb and Janssen Pharmaceuticals. P.G.R. has served on advisory boards for Celgene, Novartis and Takeda. S.L. has consulted for Takeda, Celgene, Novartis, Janssen, GSK, Bristol-Myers Squibb and Merck. R.Z.O. has served on advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Juno Therapeutics, Kite Pharma and Millennium: The Takeda Oncology Company. The remaining authors declare no competing financial interests.

**Authorship**
Contribution: J.L.K, J.J.S., S.L. and R.O. designed the study and supervised its conduct and the data analysis; J.L.K., J.P.L, J.J.S., R.D.H., L.T.H., A.K.N., S.L., R.O. and P.R. recruited patients in the source studies and provided relevant data; R.M. collected, assembled, and analyzed the data; R.M. performed the statistical analysis; J.L.K. and R.M. drafted the initial manuscript; all authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit the manuscript for publication.

**Funding**
No funding was provided for the publication of this contribution.

**Trial registration**
Clinicaltrials.gov identifier: NCT01038388

Original research article
Number of words (main text and clinical practice points): 2967
Number of references: 24
Number of tables: 4
Number of figures: 1 (see also the attached .tiff file)

## Summary

**Introduction**. Bortezomib plus lenalidomide and dexamethasone (VRD) is a standard induction therapy for newly diagnosed multiple myeloma (NDMM) patients. Given preclinical and clinical data suggesting the synergistic activity of the histone deacetylase inhibitor vorinostat with both bortezomib and lenalidomide for the treatment of MM, we hypothesized that adding vorinostat to VRD (R2V2) would increase the rate and the quality of responses to induction treatment. Here we report the results of a phase I trial (NCT01038388) evaluating R2V2 as upfront treatment for NDMM patients.

**Methods**. R2V2 was tested as induction therapy in a dose-escalation, phase 1 study in 30 NDMM patients deemed eligible for autologous stem-cell transplantation (ASCT). Treatment consisted of 4 induction cycles with R2V2 followed by either ASCT or 4 additional R2V2 cycles and lenalidomide maintenance.

**Results**. The maximum tolerated dose of vorinostat was 200 mg daily. Most common adverse events were gastrointestinal (87%), fatigue and peripheral neuropathy (60%) and thrombocytopenia (33%). R2V2 induced an objective response in 96% of patients, with 48% who achieved at least a complete remission. Median progression-free survival was 52 months, with 77% of patients alive at 5 years.

**Conclusion**. R2V2 as induction treatment for NDMM patients resulted in remarkable response rates at the cost of increased toxicity.


## Micro-Abstract

This phase I study aimed to determine the maximum tolerated dose, activity and tolerability of vorinostat plus bortezomib-lenalidomide-dexamethasone (R2V2) as induction therapy for newly diagnosed multiple myeloma.

R2V2 resulted in remarkable response rates at the cost of increased toxicity.

Future studies will identify the best partner for the standard bortezomib-lenalidomide-dexamethasone combination.


## Keywords

newly diagnosed multiple myeloma; vorinostat; bortezomib; lenalidomide; dexamethasone

## INTRODUCTION

In the last decades, the introduction of several anti-myeloma compounds belonging to different drug classes has resulted into a dramatic survival improvement in multiple myeloma (MM) patients.[1] In newly diagnosed (ND)MM, the eligibility for autologous stem-cell transplantation (ASCT) is the major driver of treatment choice.[2] Patients who are considered eligible for high-dose melphalan and ASCT usually receive a limited number of induction cycles (e.g. 4 to 6) before stem-cell collection, high-dose chemotherapy and ASCT. The aim of induction therapy for NDMM patients is to attain a deep response, as the achievement of a complete remission (CR) has been shown to prolong both progression-free survival (PFS) and overall survival (OS).[3,4] More recently, it has been shown that the real value of CR relies in the achievement of the minimal residual disease (MRD) status,[5] which correlates with better PFS and OS. Obtaining a deep and durable response with front-line therapies is therefore of utmost importance. The combination of bortezomib with an immunomodulatory drug (IMiD) – either thalidomide (VTD)[6] or lenalidomide and dexamethasone (VRD) – represents the standard induction approach for transplant-eligible NDMM patients.[1] Despite the efficacy of such triplets, the rate of patients who are able to obtain a CR after the induction phase ranges from 14 to 23%. To further improve the efficacy of VRD, the addition of a fourth drug has been explored with promising efficacy.[7–9]

In a phase I study, a 4-drug combination including panobinostat (a histone deacetylase inhibitor, HDACi) and VRD proved to be safe and effective as upfront therapy in transplant-eligible MM patients.

Given preclinical and clinical data suggesting a synergistic activity of the HDAci vorinostat with bortezomib and lenalidomide, we hypothesized that adding vorinostat to VRD (R2V2) would increase the rate and the quality of response to induction treatment.[10–13]

Here we report the results of a phase I trial evaluating R2V2 as upfront treatment for NDMM patients.

## METHODS

*Patient Population*

NDMM patients who were aged 18 years or older, required treatment, and had received no previous systemic anti-MM therapy (except corticosteroids for hypercalcemia or spinal cord compression, not exceeding 160 mg of dexamethasone or equivalent) were eligible. Patients were excluded if they had grade 2 or greater peripheral neuropathy (PN), a serum creatinine clearance less than 60 ml/min, signs of bone marrow failure (hemoglobin less than 8.0 g/dL; platelets less than 50.000/L; absolute neutrophil count less than 1000/L), transaminase levels elevated 2 or more times the upper limit of normal, myocardial infarction within 6 months prior to enrolment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina or active conduction system abnormalities, or other specific significant comorbidities.

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice. Review boards at all the participating institutions approved the study. All patients provided written informed consent.

*Study design and treatment*

This was an open-label phase I study conducted at 3 centers in the United States, with enrolment between January 2010 and May 2012. The primary endpoint was to determine the maximum tolerated dose (MTD) of vorinostat with lenalidomide, bortezomib and dexamethasone; secondary endpoints included the rate of CR plus partial response (PR) after cycle 4 and cycle 8, the rate of very good partial response (VGPR) or better, time to progression (TTP), PFS, OS, and toxicity.

Treatment consisted of an induction and a maintenance phase. Induction consisted of eight 3-week treatment cycles of oral (PO) vorinostat, at different doses according to dose cohorts, from 100 mg up to 400 mg, continuously on day 1 to 14; oral lenalidomide (25 mg) on days 1 to 14; intravenous bortezomib (1.3 mg/m$^2$) on days 1, 4, 8, and 11; oral dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12. Patients who achieved at least a PR were allowed to proceed to ASCT after a minimum of 4 induction cycles. After the 8th cycle, responding patients could receive maintenance therapy comprising 3-week cycles of lenalidomide on days 1 to 14 at the dose level tolerated at the end of cycle 8, and/or bortezomib on days 1 and 8 plus dexamethasone (10 mg) on days 1, 2, 8, and 9.

Deep-vein thrombosis prophylaxis with aspirin (81 or 325 mg daily) or alternative anticoagulation was mandatory.

*Dose escalation and determination of maximum tolerated dose*

The aim of this phase I trial was to determine the MTD of vorinostat administered in combination with fixed doses of lenalidomide, bortezomib and dexamethasone. The MTD was defined to be the dose of vorinostat that resulted in a probability, equal to $\theta=0.33$, that a dose-limiting toxicity (DLT) occurred within 1 cycle of therapy.

The dose escalation followed a Bayesian method, known as EWOC (Escalation With Overdose Control), allowing a precise determination of the therapeutic working dose while directly controlling the likelihood of an overdose.

The dose for the first cohort of 2 patients in the trial was vorinostat at 100 mg PO. The dose for each subsequent cohort was determined so that, on the basis of all the available data, the probability that it exceeded the MTD would be equal to a pre-specified value $\alpha$. In this trial, we started at $\alpha=0.25$ and increased $\alpha$ in small increments of 0.05 until $\alpha=0.5$, this value being a compromise between the therapeutic efficacy of vorinostat and its safety profile. The dose selected for every patient in the trial ranged between the minimum dose of 100 mg and the maximum allowable dose of 400 mg. The trial was to be terminated in case of an excessive number of dose-related toxicities observed early in the trial, at the discretion of the principal investigator.

A maximum of 30 patients were to be accrued in the trial. Upon completion of the trial, the MTD was estimated as the median of the marginal posterior distribution of the MTD.

A DLT was defined as a grade 3 or greater non-hematologic toxicity (except for nausea/vomiting and fatigue responding to maximal treatment and alopecia), or a grade 4 hematologic toxicity (including grade 4 thrombocytopenia or platelet count <25,000/μL of any duration, failure of absolute neutrophil count to recover to ≥1,000/μL or platelets to ≥50,000/μL within 14 days of the last treatment), or inability to receive therapy on day 1, cycle 2 because of persisting drug-related toxicity from cycle 1.

*Safety and response criteria*

According to the European Bone Marrow Transplant (EBMT) Response Criteria, responses were recorded at the beginning of every cycle. Both near-complete response (nCR) and VGPR were evaluated.[14,15]

All adverse events (AEs) were assessed during each cycle and graded according to the National Cancer Terminology Criteria for Adverse Events (version 3.0).[16] According to the International Myeloma Working Group (IMWG), high-risk cytogenetics were defined by the presence of at least one chromosomal alteration among del17p, t(4;14) or t(14;16).[17]

*Statistical analysis*

All patients who received at least 1 dose of study drugs were evaluated for toxicity and survival analysis. Patients who completed at least 1 cycle were evaluable for response.

Patient and disease characteristics were summarized using descriptive statistics. Time to response was calculated from the start of treatment to the date of the first response (CR, nCR, VGPR, PR). TTP was calculated from the date of entry into the trial to the date of progression. PFS was calculated from the date of entry into the trial to the date of progression or death or the date the patient was last known to be in remission. OS was calculated from the date of entry into the trial to the date of death or the date the patient was last known to be alive. Time-to-event data were analyzed using the Kaplan–Meier method. The individual effect on TTP, PFS and OS of the International Staging System (ISS stage I vs. II/III) was evaluated using Cox proportional hazards models.

Results are presented as hazard ratios (HRs) and 95% confidence intervals (95% CIs). Data were analyzed as of December, 2017 using R (Version 3.1.1).

## RESULTS

*Patients*

Between January 2010 and May 2012, 30 patients were enrolled at 3 US centers. Patient characteristics are listed in *Table 1*. The median age at diagnosis was 54 years (range, 39-75).

Forty-three % of patients presented with ISS stage II or III, while high-risk fluorescence in situ hybridization (FISH, including t(4;14), t(14,16) or del17p) was present in 17% of patients.
Twenty-four patients completed 4 induction cycles, whereas 6 patients discontinued induction because of toxicity (n=3), death (n=1), lack of compliance (n=1), and consent withdrawal (CW, n=1). After cycle 4, 9 patients proceeded to ASCT. Twelve patients completed 8 induction cycles; of them, 11 started maintenance. Nine patients discontinued maintenance because of PD (n=6), to proceed to ASCT (n=2) and because of CW (n=1). At the data cut-off (December 2017), 2 patients are still on treatment.

*MTD*

One DLT was observed in each of the first 2 cohorts with vorinostat at 100 and 200 mg, respectively (cohort 1: grade 3 syncope; cohort 2: grade 3 liver function test [LFT] increase) (*Table 2*). No DLTs were reported in the third cohort with vorinostat at a dose of 300 mg. In the fourth cohort (vorinostat 400 mg), 3/3 patients experienced a DLT: grade 4 thrombocytopenia, sudden death and grade 3 syncope. Vorinostat was de-escalated to 300 mg with 2 further DLTs: 1 grade 4 LFT increase and 1 grade 3 creatinine increase. Vorinostat was further de-escalated, with 11 patients receiving vorinostat at 200 mg; 4 DLTs were observed: 2 grade 4 pulmonary embolisms (PEs), 1 grade 3 LFT increase and 1 grade 3 hyperglycemia (in a patient with a history of type 2 diabetes). The MTD of vorinostat in combination with VRD was determined to be 200 mg.

*Safety*

All patients (n=30) were evaluable for safety. At least 1 hematologic, treatment-related adverse events (TRAEs) of any grade were reported in 43% of patients: thrombocytopenia, anemia and neutropenia were observed in 33%, 20%, and 7% of patients, respectively (*Table 1*).
Non-hematologic TRAEs of any grade and of grade 3-5 occurred in 100% and 63% of patients, respectively. The most common non-hematologic, any-grade TRAEs were: diarrhea (64%), nausea (57%), constipation (50%), LFT elevation (33%), and rash (33%). Any-grade sensory and motor PNs were reported in 60% and 23% of patients, respectively, with limited grade 3-4 events (3% and 0, respectively).

Nineteen patients (63%) required ≥1 dose reductions: vorinostat was reduced in 33%, lenalidomide in 23%, bortezomib in 47% and dexamethasone in 43% of patients, respectively. The most common reasons for dose reduction were LFT increase for vorinostat and lenalidomide, and PN, hand tremor and mood alteration for bortezomib and dexamethasone.
Induction treatment was discontinued in 5 patients (17%) due to toxicity: sudden death (n=1), myocardial infarction (n=1), PE (n=1), grade 3 PN (n=1) and grade 3 hypercalcemia (n=1).

*Efficacy*

Twenty-seven patients completed the first cycle and were evaluable for response (*Figure 1*).
The median number of cycles administered was 4.5 (1-106). The best response was ≥partial response (≥PR) in 96% of patients; 74% of patients achieved ≥very good PR (≥VGPR) and 48%

≥CR. After the 4th cycle, the rates of ≥PR, ≥VGPR and ≥CR were 96%, 59% and 19%, respectively. Among patients who completed 8 induction cycles (n=12), the ≥PR, ≥VGPR and ≥CR rates were 100%, 83% and 25%, respectively.

Overall, the rates of ≥PR and ≥CR were similar between ISS I (94% and 50%) and ISS II/III (100% and 50%) patients, as well as between standard-risk (90% and 60%) and high-risk FISH patients (100% and 40%).

After a median follow-up of 63 months (range 0-93 months), 8 patients (27%) progressed while 5 patients (17%) died (3 for progressing myeloma, 1 due to sudden death at cycle 1 and 1 for colorectal cancer).

The median TTP was not reached (NR, 5-year TTP: 66%). The median PFS was 52 months, with 46% of patients free from progression or death at 5 years (95% CI 0.29-0.73) (*Figure 1*). The median OS was NR; at 5 years, 77% of patients were alive (95% CI 0.59-0.97). No difference was found in terms of median TTP (66 months vs. NR, p=not significant [ns]), PFS (58 vs. 51 months, p=ns) and OS (NR vs. NR, p= ns) in patients with ISS stage I as compared to those with ISS stage II/III disease.

## DISCUSSION

This is the first trial to combine vorinostat with VRD in a quadruplet induction regimen as initial treatment for transplant-eligible NDMM patients. The addition of vorinostat, at the MTD of 200 mg, VRD proved to be highly active, inducing rapid and deep responses, despite an increase in the rate of AEs as compared to VRD alone[18,19]

The MTD of vorinostat combined with VRD was 200 mg. Vorinostat was safely escalated up to the dose of 400 mg, at which 3 out of 3 patients experienced a DLT. Consequently, vorinostat had to be de-escalated to 200 mg, which was defined as the MTD. This dose was inferior to doses of vorinostat in combination with either bortezomib (300-400 mg) or lenalidomide-dexamethasone (400 mg) in previous trials.[20–22] Three out of 11 DLTs were due to LFT increases and 2 due to PEs; while the former could be attributable to a cumulative toxicity from all the study drugs, thromboembolic events are common with lenalidomide, despite adequate prophylaxis.

TRAEs were mainly mild to moderate (grade 1-2) and grade 3-4 TRAEs were infrequent. R2V2 displayed a higher rate of thrombocytopenia (33%) as compared to VRD (14-18%),[18,19] though inferior to that reported with other 4-drug, VRD-based regimens.[7–9] As expected, the most frequent non-hematologic AEs were gastro-intestinal (GI). The addition of vorinostat to VRD increased the rate of any-grade diarrhea (64% vs 35%) and nausea/vomiting (57% vs 32%) as compared to VRD, though GI events were mainly of grade 1-2.

The rates of any-grade PNs, both sensory (60%) and motor (23%), were in line with those reported with VRD, with bortezomib administered intravenously.[7,8,18]

Multiple factors could have impaired the tolerability of this 4-drug regimen: the overlapping safety profile of vorinostat and bortezomib in terms of thrombocytopenia, GI and hepatic AEs, (similar to the results of VANTAGE and PANORAMA trials)[21,23] or the intravenous administration of bortezomib (since the protocol was designed before the adoption of

subcutaneous administration). Finally, a different schedule of vorinostat, such as the 1-week-on/1-week-off one, could improve tolerability.

R2V2 provided rapid and deep responses. By the 4th cycle, higher rates of ≥PR (96%), ≥VGPR (63%) and ≥CR (17%) were observed with R2V2 as compared to VRD (75%, 11% and 6%, respectively),[18] in line with those reported with VRDD (96%, 51% and 21%, respectively).[8] Responses further deepened in patients treated up to 8 cycles.

Of note, R2V2 was also effective in high-risk patients, as the ≥PR and ≥CR rates were similar between standard-risk (90% and 60%) and high-risk FISH patients (100% and 40%).

Several attempts to build on VRD have been made through the addition of a 4th drug like cyclophosphamide, doxorubicin and panobinostat, with promising results, though at the cost of increased toxicity.[7,8,24] Monoclonal antibodies, with their unique safety profile and tolerability, represent perfect candidates for a quadruplet regimen based on bortezomib plus an IMiD. The anti-CD38 monoclonal antibody daratumumab combined with standard VTD increased the depth of response obtained after the induction and consolidation phases, as compared to standard VTD, thus significantly prolonging PFS. Similar results were reported with daratumumab when combined with VRD (D-VRD) in a phase II study. D-VRD increased the overall response rate (99% vs. 92%) as well as the rate of CR (52% vs 42%), as compared to VRD. Combining daratumumab to VRD added limited toxicity as compared to VRD, mainly in terms of neutropenia (49% vs. 31%) and infections (82% vs. 55%).[9]

## CONCLUSION

In conclusion, this study provided evidence for the development of a 4-drug regimen based on VRD as induction treatment for NDMM patients. R2V2 induced rapid and deep responses, at the cost of increased toxicity. An alternative schedule of vorinostat, along with a subcutaneous administration of bortezomib, could increase the tolerability of this combination and allow higher doses of vorinostat. The merits of a 4-drug induction chemotherapy must be weighed against the potential risks, and further studies are necessary to define the best partners for standard VRD. Taking into consideration the positive results in terms of both efficacy and safety observed combining VRD with an anti-CD38 monoclonal antibody, 4-drug regimens based on a monoclonal antibody are likely to become the standard first-line approach for MM patients.

## CLINICAL PRACTICE POINTS

Bortezomib, lenalidomide and dexamethasone (VRD) is a standard induction regimen for newly-diagnosed multiple myeloma (NDMM) patients. Despite the efficacy shown by VRD induction in terms of cytoreduction, only a fraction of patients achieves a complete response after the usual 4 induction cycles. This evidence highlights the need for more effective induction strategies.

Given preclinical and clinical data suggesting the synergistic activity of the histone deacetylase inhibitor vorinostat with bortezomib and lenalidomide, we hypothesized that adding vorinostat to VRD (R2V2) would increase the rate and the quality of responses of the induction treatment. We tested this hypothesis in a phase I study to determine the maximum tolerated

dose (MTD) of vorinostat in combination with VRD and the efficacy and safety of this quadruplet regimen.

The MTD of vorinostat combined with VRD was 200 mg. R2V2 proved to be highly effective, with 96% of patients achieving an objective response after 4 induction cycles, 17% of them being in CR. Most common adverse events were gastrointestinal (87%), fatigue and peripheral neuropathy (60%) and thrombocytopenia (33%).

This study showed that the addition of a 4th drug with a different mechanism of action to VRD can increase the rate and depth of responses obtained with VRD. Monoclonal antibodies, in particular the anti-CD38 ones, with their unique safety profile that does not overlap with immunomodulatory agents and proteasome inhibitors, are ideal partners for VRD and will be incorporated in induction regimens.

## References


1. Kumar SK, Callander NS, Alsina M, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. *J Natl Compr Canc Netw*. 2018;16(1):11-20. doi:10.6004/jnccn.2018.0002
2. Mina R, Lonial S. Is there still a role for stem cell transplantation in multiple myeloma? *Cancer*. 2019;125(15):2534-2543. doi:10.1002/cncr.32060
3. Lahuerta JJ, Mateos MV, Martínez-López J, et al. Influence of Pre- and Post-Transplantation Responses on Outcome of Patients With Multiple Myeloma: Sequential Improvement of Response and Achievement of Complete Response Are Associated With Longer Survival. *J Clin Oncol*. 2008;26(35):5775-5782. doi:10.1200/JCO.2008.17.9721
4. van de Velde HJK, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica*. 2007;92(10):1399-1406. doi:10.3324/haematol.11534
5. Lahuerta J-J, Paiva B, Vidriales M-B, et al. Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials. *J Clin Oncol*. 2017;35(25):2900-2910. doi:10.1200/JCO.2016.69.2517
6. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol*. 2017;28(suppl_4):iv52-iv61. doi:10.1093/annonc/mdx096
7. Kumar SK, Flinn I, Noga SJ, et al. Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: phase 1 results from the multicenter EVOLUTION study. *Leukemia*. 2010;24(7):1350-1356. doi:10.1038/leu.2010.116
8. Jakubowiak AJ, Griffith KA, Reece DE, et al. Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: a phase 1/2 Multiple Myeloma Research Consortium trial. *Blood*. 2011;118(3):535-543. doi:10.1182/blood-2011-02-334755
9. Voorhees P, Kaufman JL, Laubach J, et al. Daratumumab + Lenalidomide, Bortezomib &

Dexamethasone Improves Depth of Response in Transplant-eligible Newly Diagnosed Multiple Myeloma: GRIFFIN. 17th International Myeloma Workshop [IMW] Abstract Book. :546-547 [Abstract #OAB-87].

10. Hideshima T, Bradner JE, Wong J, et al. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. *Proc Natl Acad Sci*. 2005;102(24):8567-8572. doi:10.1073/pnas.0503221102

11. Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and  -tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood*. 2006;108(10):3441-3449. doi:10.1182/blood-2006-04-016055

12. Bilotti E, Vesole DH, McBride L, et al. Vorinostat in Combination With Lenalidomide and Dexamethasone in Lenalidomide-Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. 2016;16(10):558-562. doi:10.1016/j.clml.2016.08.001

13. Badros A, Philip S, Niesvizky R, et al. Phase I Trial of Suberoylanilide Hydroxamic Acid (SAHA) + Bortezomib (Bort) in Relapsed Multiple Myeloma (MM) Patients (pts). *Blood*. 2007;110(11):Abstract #1168 [ASH 49th Annual Meeting]. http://www.bloodjournal.org/content/110/11/1168. Accessed August 16, 2018.

14. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102(5):1115-1123. doi:10.1046/j.1365-2141.1998.00930.x

15. Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473. doi:10.1038/sj.leu.2404284

16. National Cancer Institute [USA]. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Cancer Therapy Evaluation Program. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Published 2006.

17. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962. doi:10.1182/blood-2016-01-631200

18. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood*. 2010;116(5):679-686. doi:10.1182/blood-2010-02-268862

19. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med*. 2017;376(14):1311-1320. doi:10.1056/NEJMoa1611750

20. Siegel DS, Dimopoulos M, Jagannath S, et al. VANTAGE 095: An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination With Bortezomib in Patients With Relapsed and Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. 2016;16(6):329-334.e1. doi:10.1016/j.clml.2016.02.042

21. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol*. 2013;14(11):1129-1140. doi:10.1016/S1470-2045(13)70398-X

22. Sanchez L, Vesole DH, Richter JR, et al. A phase IIb trial of vorinostat in combination with lenalidomide and dexamethasone in patients with multiple myeloma refractory to previous lenalidomide-containing regimens. *Br J Haematol*. 2017;176(3):440-447.

doi:10.1111/bjh.14429

23. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood*. 2013;122(14):2331-2337. doi:10.1182/blood-2013-01-481325

24. Shah JJ, Feng L, Manasanch EE, et al. Phase I/II Trial of the Efficacy and Safety of Combination Therapy with Lenalidomide/Bortezomib/Dexamethasone (RVD) and Panobinostat in Transplant-Eligible Patients with Newly Diagnosed Multiple Myeloma. *Blood*. 2015;126(23):Abstract #187 [ASH 57th Annual Meeting]. http://www.bloodjournal.org/content/126/23/187. Accessed August 16, 2018.

**Table 1**. Patient characteristics

| | All<br>N= 30<br>(%) |
|---|---|
| Age | |
| Median-years (range) | 54 (39-75) |
| ≥65 | 6 (20) |
| Sex | |
| Female | 11 (37) |
| Male | 19 (63) |
| Race | |
| White | 21 (70) |
| African-American | 6 (20) |
| Other | 3 (10) |
| ECOG | |
| 0 | 8 (27) |
| 1 | 19 (63) |
| 2 | 3 (10) |
| MM subtype | |
| IgG | 2 (70) |
| IgA | 8 (27) |
| Light chain | 1 (3) |
| International staging system | |
| I | 17 (57) |
| II | 10 (33) |
| III | 3 (10) |
| FISH* | |
| Standard risk | 13 (43) |
| High risk | 5 (17) |
| Missing | 12 (40) |
| Bone marrow invasion | |
| Plasma cell % | 40% (1-90%) |
| Bone involvement | |
| Yes | 25 (83) |
| No | 5 (17) |

*High-risk FISH is defined by the presence of one of the following cytogenetic abnormalities: del17p, t(4;14) or t(14;16).

**Abbreviations.** ECOG, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridization.

**Table 2**. Dose-limiting toxicities (DLTs)

| **Dose limiting toxicities** n=30 | | | |
|---|---|---|---|
| *Dose level* | *Vorinostat (mg)* | *Patients (n)* | *DLT* |
| 1 | 100 | 4 | G3 syncope |
| 2 | 200 | 4 | G3 LFT |
| 3 | 300 | 6 | - |
| 4 | 400 | 3 | G4 thrombocytopenia<br>Sudden death<br>G3 syncope |
| 3 | 300 | 2 | G3 creatinine increase<br>G4 LFT elevation |
| 2 | 200 | 11 | G4 pulmonary embolism (n=2)<br>G3 LFT elevation<br>G3 hyperglycemia |

**Abbreviations**. n, number; G, grade; LFT, liver function test.

**Table 3.** Any-grade, treatment-related adverse events (AEs) during the induction phase (cycles 1-8)

| **Adverse Events** n=30 (%) | | |
|---|---|---|
| *Events* | *Any grade* | *Grade 3-4* |
| Hematologic | | |
| ≥ 1 event | 13 (43) | 6 (20) |
| Anemia | 6 (20) | 1 (3) |
| Thrombocytopenia | 10 (33) | 4 (13) |
| Neutropenia | 2 (7) | 2 (7) |
| Gastrointestinal (≥1 event) | 26 (87) | 2 (7) |
| Nausea | 17 (57) | 1 (3) |
| Diarrhea | 19 (64) | 1 (3) |
| Constipation | 15 (50) | - |
| Dyspepsia | 5 (17) | - |
| General (≥1 event) | 27 (90) | 7 (23) |
| Fatigue | 18 (60) | 4 (7) |
| Peripheral Edema | 10 (33) | 1 (3) |
| Electrolytes imbalance | 13 (43) | 2 (7) |
| Dizziness | 10 (33) | 1 (3) |
| Hyperglycemia | 3 (10) | 1 (3) |
| Fever | 2 (7) | 2 (7) |
| Neurological (≥1 event) | 23 (77) | 2 (7) |
| Neuropathy, sensitive | 18 (60) | 1 (3) |
| Neuropathy, motor | 7 (23) | - |
| Anxiety | 5 (17) | 1 (3) |
| Tremor | 4 (13) | 1 (3) |
| Infection (≥1 event) | 10 (33) | 2 (7) |
| Upper respiratory tract infection | 5 (17) | 2 (7) |
| Hepatic (≥1 event) | 10 (33) | 4 (13) |
| Liver enzymes increase | 10 (33) | 4 (13) |
| Bilirubin increase | 3 (10) | - |
| Dermatological (≥1 event) | 9 (30) | - |
| Rash | 9 (30) | - |
| Vascular (≥1 event) | 7 (23) | 4 (13) |
| Hypotension | 4 (13) | 1 (3) |
| Syncope | 2 (7) | 2 (7) |
| Pulmonary embolism | 2 (7) | 2 (7) |
| Pulmonary (≥1 event) | 6 (20) | - |
| Dyspnea | 4 (13) | - |
| Cough | 2 (7) | - |
| Cardiac (≥1 event) | 4 (13) | 2 (7) |
| Cardio-pulmonary arrest | 1 (3) | 1 (3) |
| NSTEMI | 1 (3) | 1(3) |
| Atrial fibrillation | 1 (3) | - |
| QT-prolongation | 1 (3) | - |
| Renal (≥1 event) | 2 (7) | 1 (3) |
| Creatinine increase | 2 (7) | 1 (3) |
| Other (≥1 event) | 21 (70) | 4 (13) |
| Blurred vision | 7 (23) | - |
| Pain | 6 (20) | 2 (7) |
| Insomnia | 6 (20) | - |

**Abbreviations.** NSTEMI, Non-ST elevation myocardial infarction.

**Table 4**. Best response with vorinostat-VRD

| Response | After cycle 4 n=24 | After cycle 8 n=12 | Best response n=27* |
|---|---|---|---|
| sCR | 1 (4%) | 1 (8%) | 5 (19%) |
| CR | 3 (13%) | 2 (17%) | 8 (30%) |
| VGPR | 11 (46%) | 7 (58%) | 7 (26%) |
| PR | 8 (33%) | 2 (17%) | 6 (22%) |
| SD | 0 | 0 | 0 |
| PD | 0 | 0 | 0 |
| NA | 1 (4%) | 0 | 1 (4%) |
| | | | |
| ORR | 23 (96%) | 12 (100%) | 26 (96%) |
| ≥CR | 4 (17%) | 3 (25%) | 13 (48%) |
| ≥VGPR | 15 (63%) | 10 (83%) | 20 (74%) |

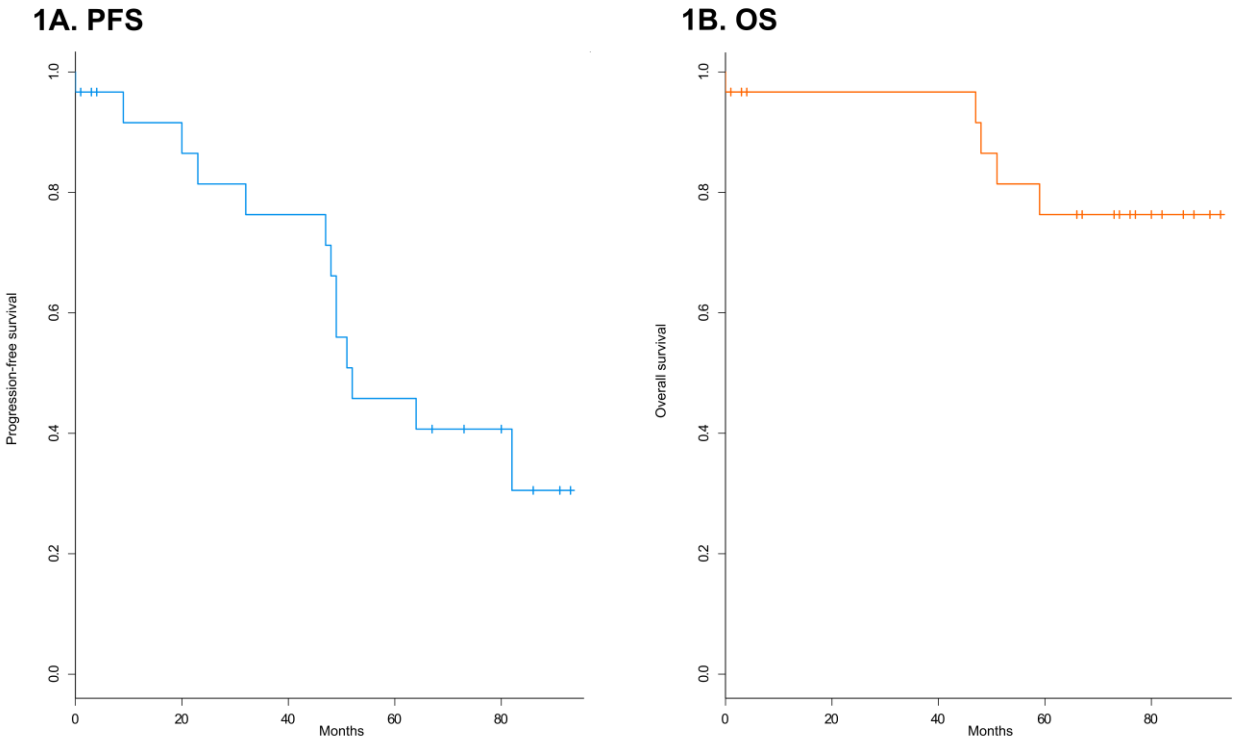
*As per protocol, patients were evaluable for efficacy if they had completed at least 1 cycle of the assigned treatment.

**Abbreviations.** VRD, bortezomib-lenalidomide-dexamethasone; CR, complete response; sCR, stringent CR; PR, partial response; VGPR, very good PR; SD, stable disease; PD, progressive disease; NA, not available; ORR, overall response rate.

**Figure Title and Legend**

**Figure 1. Vorinostat-VRD**

A) Best response with vorinostat-VRD and (B) Kaplan-Meier estimate for PFS and OS among all patients treated with vorinostat-VRD (N=30)




**Legend**.

*As per protocol, patients were evaluable for efficacy if they had completed at least 1 cycle of the assigned treatment.

VRD, bortezomib-lenalidomide-dexamethasone; OS, overall survival; PFS progression-free survival.

**A Phase I Trial Evaluating Vorinostat plus Bortezomib, Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma**

## CLINICAL PRACTICE POINTS

Bortezomib, lenalidomide and dexamethasone (VRD) is a standard induction regimen for newly-diagnosed multiple myeloma (NDMM) patients. Despite the efficacy shown by VRD induction in terms of cytoreduction, only a fraction of patients achieves a complete response after the usual 4 induction cycles. This evidence highlights the need for more effective induction strategies.

Given preclinical and clinical data suggesting the synergistic activity of the histone deacetylase inhibitor vorinostat with bortezomib and lenalidomide, we hypothesized that adding vorinostat to VRD (R2V2) would increase the rate and the quality of responses of the induction treatment. We tested this hypothesis in a phase I study to determine the maximum tolerated dose (MTD) of vorinostat in combination with VRD and the efficacy and safety of this quadruplet regimen.

The MTD of vorinostat combined with VRD was 200 mg. R2V2 proved to be highly effective, with 96% of patients achieving an objective response after 4 induction cycles, 17% of them being in CR. Most common adverse events were gastrointestinal (87%), fatigue and peripheral neuropathy (60%) and thrombocytopenia (33%).

This study showed that the addition of a 4$^{th}$ drug with a different mechanism of action to VRD can increase the rate and depth of responses obtained with VRD. Monoclonal antibodies, in particular the anti-CD38 ones, with their unique safety profile that does not overlap with immunomodulatory agents and proteasome inhibitors, are ideal partners for VRD and will be incorporated in induction regimens.

**A Phase I Trial Evaluating Vorinostat plus Bortezomib, Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma**

**Micro-Abstract**

This phase I study aimed to determine the maximum tolerated dose, activity and tolerability of vorinostat plus bortezomib-lenalidomide-dexamethasone (R2V2) as induction therapy for newly diagnosed multiple myeloma.

R2V2 resulted in remarkable response rates at the cost of increased toxicity.

Future studies will identify the best partner for the standard bortezomib-lenalidomide-dexamethasone combination.