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

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1  
2 **A Phase I Trial Evaluating Vorinostat plus Bortezomib, Lenalidomide and**  
3 **Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma**  
4  
5

6 **Running title:** Vorinostat-VRD for Newly Diagnosed Myeloma  
7  
8

9 Jonathan L. Kaufman<sup>1\*</sup>, Roberto Mina<sup>1\*</sup>, Jatin J. Shah<sup>2</sup>, Jacob P. Laubach<sup>3</sup>, Ajay K. Nooka<sup>1</sup>, Colleen  
10 Lewis<sup>1</sup>, Charise Gleason<sup>1</sup>, Cathy Sharp<sup>1</sup>, R. Donald Harvey<sup>1</sup>, Leonard T. Heffner<sup>1</sup>, Paul  
11 Richardson<sup>3</sup>, Sagar Lonial<sup>1</sup>, and Robert Z. Orlowski<sup>4</sup>  
12

13 *\*JLK and RM equally contributed to the manuscript and share the first authorship.*  
14

15 <sup>1</sup> Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, US-GA.

16 <sup>2</sup> Currently employed by Karyopharm Therapeutics, Newton, US-MA.

17 <sup>3</sup> LeBow Institute for Myeloma Therapeutics and Jerome Lipper Center for Multiple Myeloma Research, Harvard  
18 Medical School, Dana-Farber Cancer Institute, Boston, US-MA.

19 <sup>4</sup> Department of Lymphoma/Myeloma, The University of Texas, MD Anderson Cancer Center, Houston, US-TX  
20

21 **Corresponding Author:** Dr. Roberto Mina, MD, Hematology and Medical Oncology, Winship Cancer Institute,  
22 Emory University, 1365C Clifton Rd, Atlanta, GA 30322, USA. +1 778-4322 Email: roberto.mina.rm@gmail.com  
23

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56

57 **Summary**

58

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

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

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

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

77

78

79 **Micro-Abstract**

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

83

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

85

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

88

89 **Keywords**

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

91

92

93

94 **INTRODUCTION**

95

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

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

116 Given preclinical and clinical data suggesting a synergistic activity of the HDACi vorinostat with  
117 bortezomib and lenalidomide, we hypothesized that adding vorinostat to VRD (R2V2) would  
118 increase the rate and the quality of response to induction treatment.<sup>10-13</sup>

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

121

122

123 **METHODS**

124

125 *Patient Population*

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

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

139

#### 140 *Study design and treatment*

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

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

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

158

#### 159 *Dose escalation and determination of maximum tolerated dose*

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

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

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

176 A maximum of 30 patients were to be accrued in the trial. Upon completion of the trial, the MTD  
177 was estimated as the median of the marginal posterior distribution of the MTD.  
178 A DLT was defined as a grade 3 or greater non-hematologic toxicity (except for  
179 nausea/vomiting and fatigue responding to maximal treatment and alopecia), or a grade 4  
180 hematologic toxicity (including grade 4 thrombocytopenia or platelet count <25,000/ $\mu$ L of any  
181 duration, failure of absolute neutrophil count to recover to  $\geq$ 1,000/ $\mu$ L or platelets to  
182  $\geq$ 50,000/ $\mu$ L within 14 days of the last treatment), or inability to receive therapy on day 1, cycle  
183 2 because of persisting drug-related toxicity from cycle 1.

184

#### 185 *Safety and response criteria*

186 According to the European Bone Marrow Transplant (EBMT) Response Criteria, responses  
187 were recorded at the beginning of every cycle. Both near-complete response (nCR) and VGPR  
188 were evaluated.<sup>14,15</sup>

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

193

194

#### 195 *Statistical analysis*

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

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

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

209

210

211

## 212 **RESULTS**

213

### 214 *Patients*

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

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

225

#### 226 *MTD*

227 One DLT was observed in each of the first 2 cohorts with vorinostat at 100 and 200 mg,  
228 respectively (cohort 1: grade 3 syncope; cohort 2: grade 3 liver function test [LFT] increase)  
229 (*Table 2*). No DLTs were reported in the third cohort with vorinostat at a dose of 300 mg. In the  
230 fourth cohort (vorinostat 400 mg), 3/3 patients experienced a DLT: grade 4 thrombocytopenia,  
231 sudden death and grade 3 syncope. Vorinostat was de-escalated to 300 mg with 2 further DLTs:  
232 1 grade 4 LFT increase and 1 grade 3 creatinine increase. Vorinostat was further de-escalated,  
233 with 11 patients receiving vorinostat at 200 mg; 4 DLTs were observed: 2 grade 4 pulmonary  
234 embolisms (PEs), 1 grade 3 LFT increase and 1 grade 3 hyperglycemia (in a patient with a  
235 history of type 2 diabetes). The MTD of vorinostat in combination with VRD was determined to  
236 be 200 mg.

237

#### 238 *Safety*

239 All patients (n=30) were evaluable for safety. At least 1 hematologic, treatment-related adverse  
240 events (TRAEs) of any grade were reported in 43% of patients: thrombocytopenia, anemia and  
241 neutropenia were observed in 33%, 20%, and 7% of patients, respectively (*Table 1*).

242 Non-hematologic TRAEs of any grade and of grade 3-5 occurred in 100% and 63% of patients,  
243 respectively. The most common non-hematologic, any-grade TRAEs were: diarrhea (64%),  
244 nausea (57%), constipation (50%), LFT elevation (33%), and rash (33%). Any-grade sensory  
245 and motor PNs were reported in 60% and 23% of patients, respectively, with limited grade 3-  
246 4 events (3% and 0, respectively).

247

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

254

#### 255 *Efficacy*

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



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

262 Overall, the rates of ≥PR and ≥CR were similar between ISS I (94% and 50%) and ISS II/III  
263 (100% and 50%) patients, as well as between standard-risk (90% and 60%) and high-risk FISH  
264 patients (100% and 40%).

265 After a median follow-up of 63 months (range 0-93 months), 8 patients (27%) progressed while  
266 5 patients (17%) died (3 for progressing myeloma, 1 due to sudden death at cycle 1 and 1 for  
267 colorectal cancer).

268 The median TTP was not reached (NR, 5-year TTP: 66%). The median PFS was 52 months, with  
269 46% of patients free from progression or death at 5 years (95% CI 0.29-0.73) (*Figure 1*). The  
270 median OS was NR; at 5 years, 77% of patients were alive (95% CI 0.59-0.97). No difference  
271 was found in terms of median TTP (66 months vs. NR, p=not significant [ns]), PFS (58 vs. 51  
272 months, p=ns) and OS (NR vs. NR, p= ns) in patients with ISS stage I as compared to those with  
273 ISS stage II/III disease.

274

275

## 276 **DISCUSSION**

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

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

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

295 The rates of any-grade PNs, both sensory (60%) and motor (23%), were in line with those  
296 reported with VRD, with bortezomib administered intravenously.<sup>7,8,18</sup>

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

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

303 R2V2 provided rapid and deep responses. By the 4<sup>th</sup> cycle, higher rates of  $\geq$ PR (96%),  $\geq$ VGPR  
304 (63%) and  $\geq$ CR (17%) were observed with R2V2 as compared to VRD (75%, 11% and 6%,  
305 respectively),<sup>18</sup> in line with those reported with VRDD (96%, 51% and 21%, respectively).<sup>8</sup>

306 Responses further deepened in patients treated up to 8 cycles.

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

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

320

321

## 322 **CONCLUSION**

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

332

333

## 334 **CLINICAL PRACTICE POINTS**

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

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

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

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

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

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

453 \*High-risk FISH is defined by the presence of one of the following cytogenetic  
 454 abnormalities: del17p, t(4;14) or t(14;16).  
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456 **Abbreviations.** ECOG, Eastern Cooperative Oncology Group Performance Status; FISH,  
 457 fluorescence in situ hybridization.

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

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

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

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

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

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**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%)

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\*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.

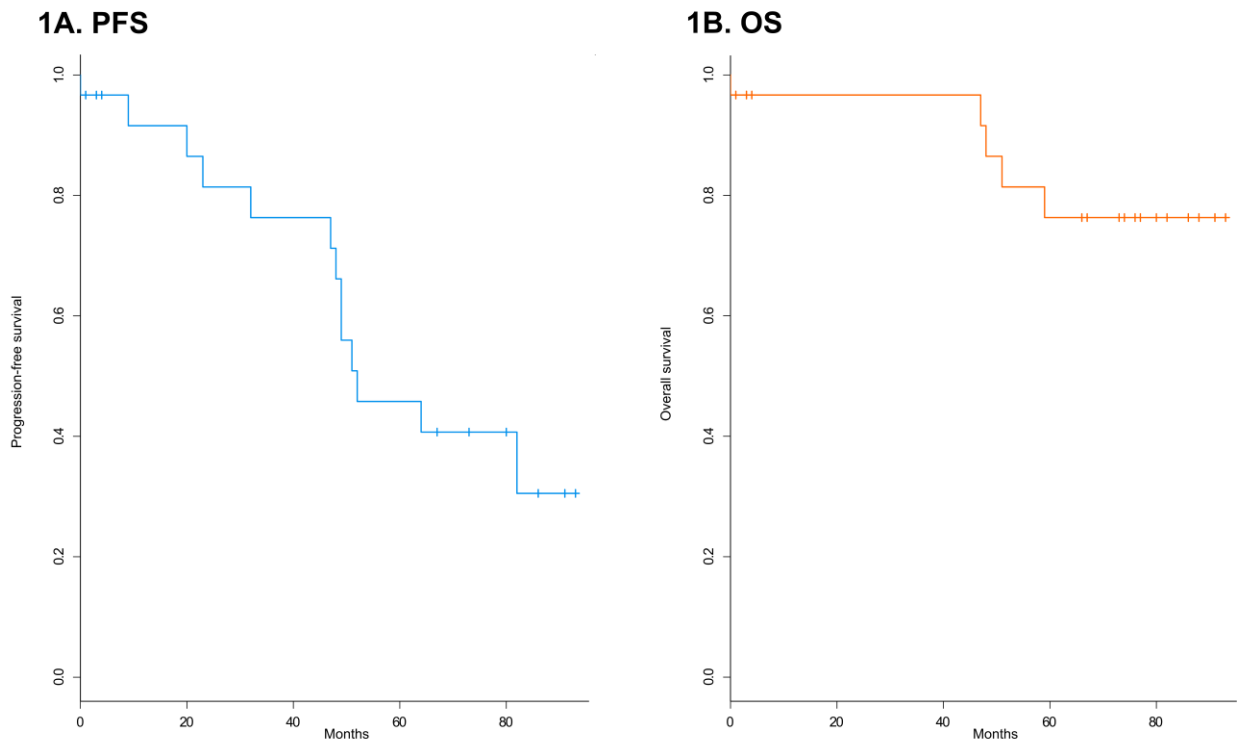
486 **Figure Title and Legend**

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488 **Figure 1. Vorinostat-VRD**

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

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494 **Legend.**

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

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

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

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503 **CLINICAL PRACTICE POINTS**

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

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

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

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

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

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531 **Micro-Abstract**

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

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

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

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