Efficacy and toxicity of histone deacetylase inhibitors in relapsed/refractory multiple myeloma: Systematic review and meta-analysis of clinical trials

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Abstract. Multiple myeloma (MM) remains incurable primarily due to relapse. Histone deacetylase inhibitors (HDACis) have shown potential application for the treatment of relapsed/refractory multiple myeloma (RRMM). To assess the efficacy and safety of HDACis in RRMM treatment, a systematic review and meta-analysis were conducted based on clinical trial data. A literature search was performed using PubMed, EMBASE, Web of Science and the Cochrane Library databases. Subsequently, 19 trials with 2193 patients treated with one of the three HDACis, panobinostat, ricolinostat and vorinostat, were identified and included in the present study. The efficacy and toxicity of each agent were assessed. The data were pooled using a random effects model in STATA 13.0. The results showed that the overall response rate (ORR) was 0.64 with a 95% confidence interval (CI) of 0.61-0.68 for panobinostat, 0.51 (95% CI, 0.46-0.55) for vorinostat and 0.38 (95% CI, 0.29-0.48) for ricolinostat. Additionally, subgroup analysis revealed an ORR of 0.36 (95% CI, 0.27-0.46) for HDACis-treated bortezomib-refractory MM patients and 0.43 (95% CI, 0.30-0.55) for lenalidomide-refractory patients. The most common grade 3 and 4 hematological adverse events were thrombocytopenia, neutropenia and anemia. Non-hematological adverse events included fatigue/asthenia, diarrhea and nausea. In conclusion, analysis of the pooled data revealed that panobinostat-containing regimens were effective and tolerable for patients with RRMM. Furthermore, lenalidomide-refractory patients may derive greater benefits from these regimens. More clinical and real-world studies are required to validate these results.

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Introduction

Multiple myeloma (MM), a malignant disease of plasma cells, is one of three major hematological malignancies with the second highest incidence rate (1). MM mostly occurs in older patients (2) and is characterized by high monoclonal immunoglobulin (also called M protein), and is often accompanied by hypercalcemia, anemia, bone and renal damage (3).

Over the past two decades, there have been new approved treatment strategies for patients with MM, including bortezomib, thalidomide or lenalidomide-containing standard regimens, which have improved the survival of patients with MM (4). However, most patients relapse after several lines of therapy, resulting in poor clinical response and survival outcomes (5). Therefore, there is an urgent need for more effective therapeutic strategies for patients with relapsed/refractory multiple myeloma (RRMM).

Histone deacetylase inhibitors (HDACis) have demonstrated antitumor activity in other hematological malignancies. For example, the HDACi vorinostat was initially approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma in 2009 (6). MM cells have an abnormal acetylated spectrum (7), which provides new insights into the application of HDACis to the treatment of MM. Basic studies have demonstrated the anti-MM activity of HDACis, which can induce apoptosis and cell cycle arrest, and degrade unfolded protein by the aggresome pathway in concert with the ubiquitin-proteasome system (8-10). Additionally, panobinostat was approved by the FDA for RRMM therapy in 2015 following the PANORAMA 2 randomized clinical trial (11). Currently, there are a number of HDACis undergoing clinical testing (12). The aim of the present study was to perform a meta-analysis to evaluate the efficacy and safety of HDACis in patients with RRMM. Additionally, a subgroup analysis was performed of patients who were bortezomib-refractory and lenalidomide-refractory to identify which patients may benefit more from the application of HDACis.

Materials and methods

Search strategies. Databases, including PubMed, EMBASE, Web of Science and the Cochrane Library were searched for clinical trials including phase I, II and III trials published between Jan 2009 and March 2018, without any language

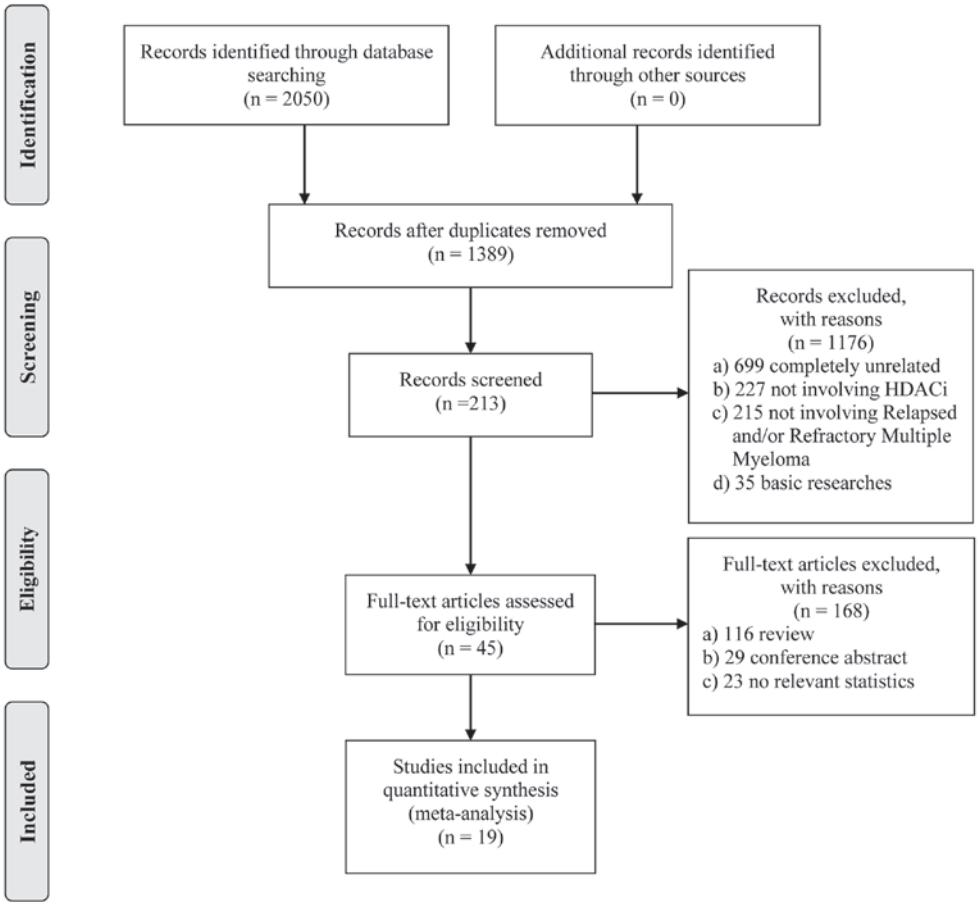

Figure 1. Flow diagram of study workflow. Basic researches, experimental research on cell lines or animals; completely unrelated, the retrieved research topic is not relevant to the present research.

restrictions. Our search criteria were based on combinations of the following keywords: 'Relapsed', 'refractory', 'multiple myeloma' and 'histone deacetylase inhibitor'.

Eligibility criteria. The eligibility criteria included: i) Patients with RRMM and intent-to-treat individuals in the studies were ≥10; ii) treatment with an HDACi, including vorinostat, panobinostat, ricolinostat; iii) the studies provided overall response rate (ORR) and/or overall survival (OS) and/or progression-free survival (PFS), as well as adverse event data which allowed statistical analysis to be performed. Additional relevant references listed in other reviews and guidelines which met all the criteria of the present study were also identified. Studies based on animal or cell line data, case reports, conference abstracts or restricted access studies were excluded.

Data extraction. Data were independently extracted by two investigators (XG and XL). Any discrepancies between the two investigators were solved by a third author (JL). The following data were extracted from all included publications and exported manually to Microsoft Excel 2016. Study name, year, therapy regimens, country, number of included patients, prior treatment lines and regimens, best response and grade 3 and 4 adverse events including anemia, neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea and nausea were recorded. Adverse affects were assessed in accordance with the Common Terminology Criteria for Adverse Events version 3.0 (13) and were classed as: Grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; grade 5, death. As the literature provided more information regarding stages 3 and 4, these were selected for examination in the current study.

Statistical analysis. A random effects model was chosen to account for the heterogeneity between the selected studies. STATA version 13.0 (StataCorp LP) was used to conduct statistical analysis. $P<0.05$ was considered to indicate a statistically significant difference. Heterogeneity was evaluated by I^2 value, and significant heterogeneity was defined as $I^2>50\%$.

Results

Literature search. In total, 213 potentially relevant studies were screened after the removal of redundant duplicates and irrelevant studies. Among the remaining articles, 168 reports were further excluded as most of them were reviews, conference abstracts or had no reported data. Following this, 45 full-text articles were evaluated in detail. Fourteen of these studies did not provide accessible data, 10 were updates for previously published data, and one study had a sample size of <10 patients. Ultimately, 19 papers met the selection criteria and were included in the meta-analysis. The flow diagram of the study design based on PRISMA 2009 (14) is presented in Fig. 1.

Table I. Baseline of 19 studies included in the present meta-analysis.

A, Panobinostat

Study	Year	Country	Phase	Regimen	Patients, n	Dosage of HDACi, mg	Median age, years (range)	(Refs.)
Isoda *et al*	2018	Japan	I	PanVd	10	10/15/20	66 (53-77)	(26)
Popat *et al*	2016	UK	I/II	PanVTd	46	10/15/20	61 (51-66)	(22)
San-Miguel *et al*	2013	US	Ib	PanV	62	10/20/25/30	62 (46-83)	(30)
Offidani *et al*	2012	Italy	II	PanMTd	12	15	73 (49-81)	(20)
					19	10	65 (40-78)	
Berdeja *et al*	2015	US	I/II	PanK	44	20/30	66 (41-82)	(23)
Berenson *et al*	2014	US	I/II	PanM	40	15/20	65 (34-88)	(24)
Richardson *et al*	2013	US	I/II	PanVd	55	20	61 (41-88)	(25)
Wolf *et al*	2012	US	II	Pan	38	20	61 (43-72)	(19)
Baertsch *et al*	2018	Ger	Real-world	PanVd	24	20	67 (49-87)	(15)
San-Miguel *et al*	2014	US	III	PanVd	387	20	63 (56-69)	(11)
				PboVd	381	-	63 (56-68)	
Chari *et al*	2017	US	II	PanRd	27	20	64 (51-75)	(18)

B, Vorinostat

Study	Year	Country	Phase	Regimen	Patients, n	Dosage of HDACi, mg	Median age, years (range)	(Refs.)
Sanchez *et al*	2016	US	IIb	VorRd	25	400	65 (48-82)	(17)
Vesole *et al*	2015	US	I	VorKRd	17	300/400	61 (48-71)	(29)
Voorhees *et al*	2017	US	I	VorVPLD	32	200/300/400	61 (39-75)	(27)
Weber *et al*	2012	US	I	VorV	34	200/300/400	61 (45-79)	(31)
Dimopoulos *et al*	2013	US	III	VorV	317	400	61 (30-85)	(16)
				PboV	320	-	63 (29-86)	
Badros *et al*	2009	US	I	VorV	23	100/200/400/500	54 (39-78)	(32)

C, Ricolinostat

Study	Year	Country	Phase	Regimen	Patients, n	Dosage of HDACi, mg	Median age, years (range)	(Refs.)
Vogl *et al*	2017	US	I/II	Rico	15	40/80/160/240/360	70 (51-79)	(21)
				RicoVd	57	40/80/160/240/360	65 (47-84)	
				RicoVd	20	≥160	65 (47-83)	
				RicoVd	24	160	67 (48-84)	
Yee *et al*	2016	US	Ib	RicoRd	38	40/80/160/240	63 (57-71)	(28)

Pan, panobinostat; V, bortezomib; d, dexamethasone; T, thalidomide; Rico, ricolinostat; R, lenalidomide; Vor, vorinostat; K, carfilzomib; PLD, pegylated-liposomal doxorubicin; M, melphalan; Ger, Germany; Pbo, placebo; -, no HDACi was administered in the placebo group.

Study characteristics. A total of 19 clinical trials with 2,193 evaluable participants treated with one of three HDACis (panobinostat, ricolinostat and vorinostat) were included in the present study. In terms of study design, there was one real-world study (15), 2 phase III studies (11,16), 4 phase II studies (17-20), 5 phase I/II studies (21-25) and 7 phase I studies (26-32). Baseline information of the included study characteristics and prior therapies are presented in Tables I and II.

Response to HDACi treatment. The extracted data were categorized into three groups in order to assess clinical efficacy based on treatment with panobinostat, ricolinostat and vorinostat. Raw data on the effectiveness of the treatment are presented in Table III, including ORR, complete response, very good partial response, partial response, median PFS, median OS and median follow-up. Analysis of the pooled data demonstrated that ORR was 0.64 (95% confidence interval [CI], 0.61-0.68; I^2, 91.5%; P<0.001) for MM patients treated with panobinostat, 0.51 (95% CI, 0.46-0.55; I^2, 81.3%; P<0.001) for those treated with vorinostat, and 0.38 (95% CI, 0.29-0.48; I^2, 85.0%; P=0.010) for patients treated with ricolinostat. The results also revealed that the

Table II. Prior treatments.

A, Panobinostat

Study	Year	Median number of prior therapies (range)	Prior regimens		PIs and iMIDs, n (%)	(Refs.)
			PIs, n (%)	iMIDs, n (%)		
Isoda *et al*	2018	3.5 (1-5)	-	-	-	(26)
Popat *et al*	2016	1 (1-4)	33 (72)	24 (52)	8 (17)	(22)
San-Miguel *et al*	2013	2 (1-10)	39 (62.9)	T: 28 (45.2) R: 28 (45.2)	-	(30)
Offidani *et al*	2012	-	8 (67)	T: 7 (58) R: 5 (42)	-	(20)
Berdeja *et al*	2015	5 (1-10)	39 (89)	39 (89)	35 (80)	(23)
Berenson *et al*	2014	4 (1-16)	2 (0-9)	-	-	(24)
Richardson *et al*	2013	4 (2-11)	55 (100)	T: 38 (69.1) R: 54 (98.2)	-	(25)
Wolf *et al*	2012	5 (-)	2 (5.3)	3 (7.9)	24 (63.2)	(19)
Baertsch *et al*	2018	5 (2-17)	V: 23 (96) K: 7 (29)	R: 23 (96) Pom: 16 (67)		(15)
San-Miguel *et al* (PANORAMA 1)	2014	1 (1-3)	169 (44)	R: 72 (19) T: 205 (53)	94 (24)	(11)
Chari *et al*	2017	3 (1-10)	V: 27 (100) K: 8 (30)	R: 27 (100) T: 6 (22) Pom: 10 (37)	-	(18)

B, Vorinostat

Study	Year	Median number of prior therapies (range)	Prior regimens		PIs and iMIDs, n (%)	(Refs.)
			PIs, n (%)	iMIDs, n (%)		
Sanchez *et al*	2016	-	20 (80)	9 (36)	-	(17)
Vesole *et al*	2015	4 (1-9)	17 (100)	16 (94)	-	(29)
Voorhees *et al*	2017	2 (1-9)	25 (78)	29 (91)	-	(27)
Weber *et al*	2012	4 (1-14)	-	T: 24 (70) R: 19 (56)	-	(31)
Dimopoulos *et al*	2013	2 (1-3)	79 (25)	192 (61)	-	(16)
Badros *et al*	2009	7 (3-13)	19 (82.6)	R: 17 (73.9) T: 23 (100)	-	(32)

C, Ricolinostat

Study	Year	Median number of prior therapies (range)	Prior regimens		PIs and iMIDs, n (%)	(Refs.)
			PIs, n (%)	iMIDs, n (%)		
Vogl *et al*	2017	5 (2-13)	V: 36 (63) K: 17 (30)	T: 12 (21) R: 38 (67)	-	(21)
Yee *et al*	2016	2 (1-3)	11 (29)	R: 12 (32) T: 4 (11)	-	(28)

PIs, Prior regimens containing proteasome inhibitors; iMIDs, Prior regimens containing immunomodulatory drugs; T, Thalidomide; R, lenalidomide; V, bortezomib; K, carfilzomib; Pom, pomalidomide; -, no data available.

Table III. Response to treatment.

A, Panobinostat

Study	Year	ORR, n (%)	CR, n (%)	VGPR, n (%)	PR, n (%)	M-PFS, months	(Refs.)
Isoda *et al*	2018	6 (60)	0 (0)	2 (20)	4 (40)	11.5	(26)
Popat *et al*	2016	42 (91)	3 (7)	21 (46)	21 (46)	15.6	(22)
San-Miguel *et al*	2013	32 (51.6)	2 (3.2)	6 (9.7)	22 (35.5)	-	(30)
Offidani *et al*	2012	5 (42.0)	0 (0)	1 (8)	4 (33.5)	8.1	(20)
Berdeja *et al*	2015	28 (67)	-	14 (33)	14 (33)	7.7	(23)
Berenson *et al*	2014	3 (7.5)	0 (0)	2 (5)	1 (2.5)	-	(24)
Richardson *et al*	2013	19 (34.5)	0 (0)	3 (5.5)	18 (32.7)	5.4	(25)
Wolf *et al*	2012	-	-	-	1 (2.6)	-	(19)
Baertsch *et al*	2018	7 (33)	0 (0)	2 (9.5)	5 (23.8)	3.5	(15)
San-Miguel *et al*	2014	235 (60.7)	42 (11)	-	128 (33)	12.0	(11)
Chari *et al*	2017	11 (41)	2 (7.4)	4 (14.8)	5 (18.5)	7.1	(18)

B, Vorinostat

Study	Year	ORR (%)	CR (%)	VGPR (%)	PR (%)	M-PFS, months	(Refs.)
Sanchez *et al*	2016	6 (24)	0 (0)	-	6 (24)	5.3	(17)
Vesole *et al*	2015	9 (53)	-	2 (12)	7 (41)	12	(29)
Voorhees *et al*	2017	20 (65)	2 (6)	7 (23)	11 (35)	13.9	(27)
Weber *et al*	2012	9 (27)	0 (0)	-	9 (27)	-	(31)
Dimopoulos *et al*	2013	177 (56.2)	25 (7.9)	-	152 (48.3)	7.6	(16)
Badros *et al*	2009	9 (42)	-	2 (9.5)	7 (33.3)	-	(32)

C, Ricolinostat

Study	Year	ORR (%)	CR (%)	VGPR (%)	PR (%)	M-PFS, months	(Refs.)
Vogl *et al*	2017	29 (29)	-	7 (7)	21 (21)	-	(21)
Yee *et al*	2016	21 (55)	2 (5)	7 (18)	10 (26)	20.7	(28)

ORR, overall response rate; CR, complete response; VGPR, very good partial response; M-PFS, median progression-free survival; -, no data available.

panobinostat-containing regimen was the most effective treatment among these three drugs according to the ORR. Forest plots are presented in Fig. 2.

Response of bortezomib and lenalidomide-refractory patients to HDACi treatment. A subgroup analysis was subsequently conducted to evaluate the effectiveness of HDACis in bortezomib-refractory and lenalidomide-refractory patients. ORR was 0.32 (95% CI, 0.24-0.40; I^2, 75.2%; P=0.001) for bortezomib-refractory patients, and 0.43 (95% CI, 0.30-0.55; I^2, 68.0%; P=0.025) for lenalidomide-refractory patients, suggesting that HDACis were better for the lenalidomide-refractory MM patients. The results are presented in Fig. 3.

Toxicity. An overview of the adverse events is presented in Table IV. Analysis of the pooled data was performed to evaluate the incidence rate of grade 3 and 4 adverse events in all included patients treated with HDACis. The most common hematological adverse events were anemia with an incidence rate of 0.13 (95% CI, 0.11-0.15; P<0.001; Fig. 4), neutropenia (0.26; 95% CI, 0.24-0.28; P<0.001; Fig. 5) and thrombocytopenia (0.37; 95% CI, 0.34-0.39; P<0.001; Fig. 6). Anemia, neutropenia and thrombocytopenia were observed at similar frequencies among panobinostat- and vorinostat-treated patients; however, ricolinostat-treated patients were affected by neutropenia more frequently than patients with anemia or thrombocytopenia. The most frequent non-hematological adverse events included fatigue/asthenia (0.18; 95% CI; 0.16-0.20; P<0.001; Fig. 7), diarrhea (0.16; 95% CI; 0.14-0.18; P<0.001; Fig. 8), and nausea (0.06; 95% CI; 0.05-0.07; P<0.001; Fig. 9).

Discussion

The recommended dose of each of the three drugs was summarized to provide a reference for future clinical practices. In the included studies, the dosages of panobinostat ranged from 10

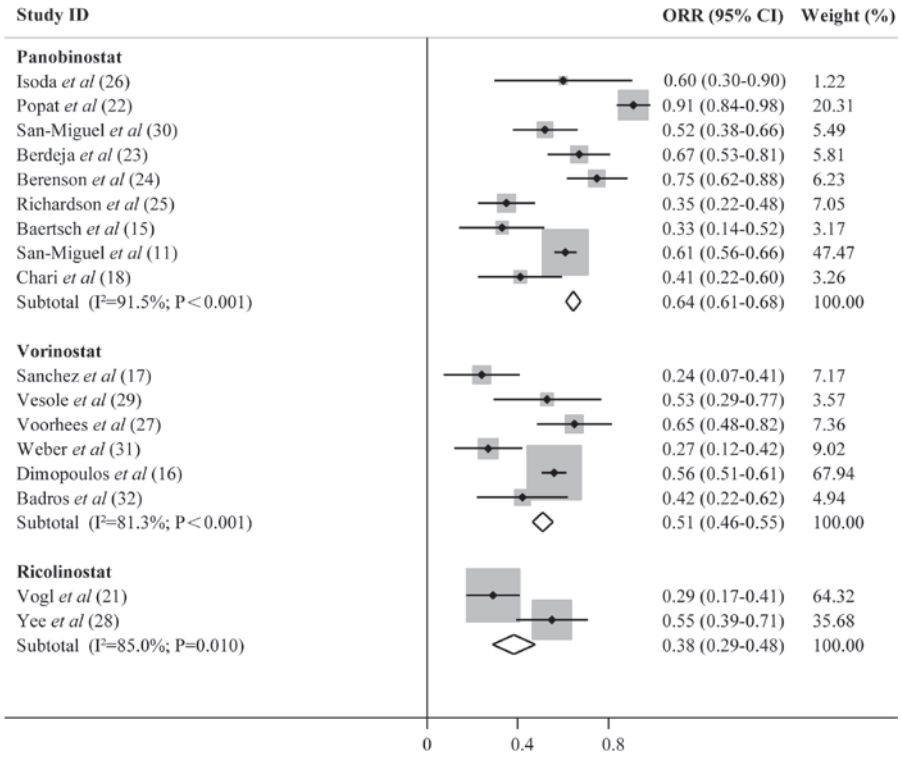

Figure 2. Overall response rate based on pooled data, and on treatment with panobinostat, ricolinostat and vorinostat in patients with relapsed/refractory multiple myeloma. The grey boxes indicate patient weight (%) and diamonds indicate a combination of the effect sizes in the subgroup.

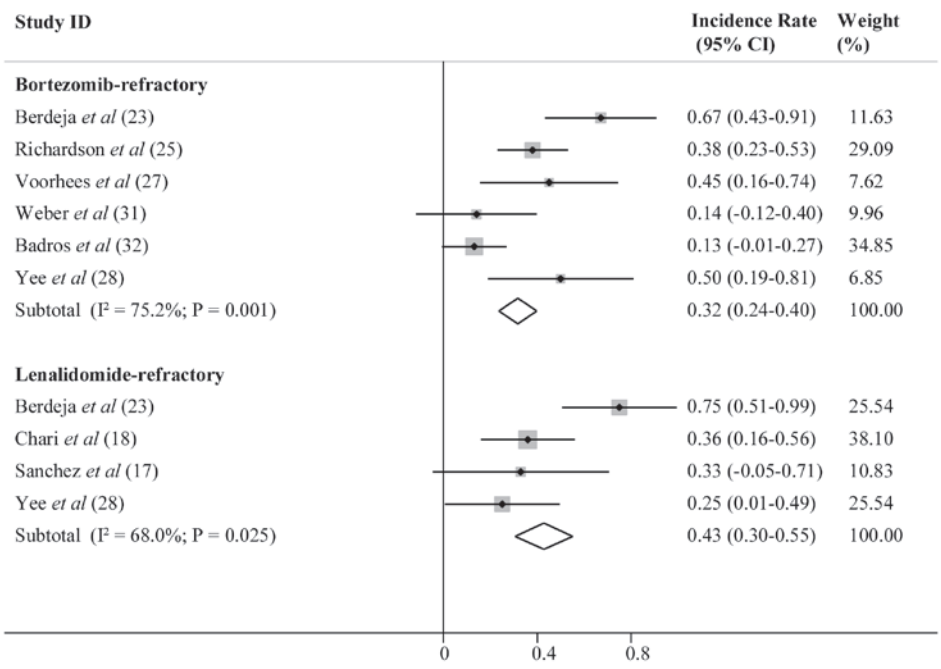

Figure 3. Overall response rate of patients with bortezomib-refractory and lenalidomide-refractory multiple myeloma treated with panobinostat, ricolinostat or vorinostat.

to 30 mg, and the maximum tolerated dose (MTD) was 20 mg, except for in a phase II clinical trial in which it was combined with melphalan, prednisone and thalidomide (20). In that study, the MTD was not determined due to the high rate of dose-limiting toxicities at doses of 10 and 15 mg (20). Additionally, the MTD was established as 30 mg when combined with carfilzomib (23). Vorinostat inhibited class I, II and IV of HDACs at doses of 100-500 mg in the selected studies, where the MTD was established at 400 mg. However, the MTD of vorinostat was not established in studies where it was combined with carfilzomib, lenalidomide and dexamethasone, or co-administered with bortezomib (29,31). In the two studies that included ricolinostat,

Table IV. HDACi treatment related grade 3 and 4 adverse events.

		Hematological			Non-hematological			
Study	Year	Anemia, n (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Fatigue/Asthenia, n (%)	Diarrhea, n (%)	Nausea, n (%)	(Refs.)
Isoda *et al*	2018	-	-	-	2 (20)	2 (20)	1 (10)	(26)
Popat *et al*	2016	3 (5)	15 (26)	8 (14)	-	-	0 (0)	(22)
San-Miguel *et al*	2013	11 (17.7)	37 (59.7)	50 (80.6)	7 (11.3)	10 (16.1)	1 (1.6)	(30)
Offidani *et al*	2012	2 (17)	8 (66)	5 (42)	-	-	-	(20)
Berdeja *et al*	2015	4 (9)	9 (21)	17 (38)	5 (11)	3 (7)	2 (5)	(23)
Berenson *et al*	2014	21 (52.5)	30 (75)	29 (72.5)	23 (57.5)	11 (27.5)	22 (55)	(24)
Richardson *et al*	2013	8 (14.5)	8 (14.5)	35 (63.6)	11 (20)	111 (20)	3 (5.5)	(25)
Wolf *et al*	2012	13 (34.2)	13 (34.2)	15 (39.5)	18 (47.4)	16 (42.1)	21 (55.3)	(19)
Baertsch *et al*	2018	-	-	17 (85)	4 (17)	0 (0)	-	(15)
San-Miguel *et al*	2014	-	-	-	91 (24)	97 (25)	21 (6)	(11)
Chari *et al*	2017	2 (5)	19 (59)	10 (31)	4 (12.5)	3 (9.4)	-	(18)
Sanchez *et al*	2016	5 (20)	12 (48)	8 (32)	2 (8)	1 (4)	1 (4)	(17)
Vesole *et al*	2015	7 (41)	9 (53)	9 (53)	1 (6)	0 (0)	-	(29)
Voorhees *et al*	2017	0 (0)	12 (37.5)	15 (47)	5 (16)	6 (19)	3 (9)	(27)
Weber *et al*	2012	0 (0)	3 (9)	14 (41)	7 (21)	3 (9)	3 (9)	(31)
Dimopoulos *et al*	2013	47 (15)	59 (19)	74 (23)	50 (16)	51 (16)	24 (8)	(16)
Badros *et al*	2009	-	-	-	11 (47.8)	5 (21.7)	-	(32)
Vogl *et al*	2017	11 (19)	2 (4)	21 (37)	4 (7)	3 (5)	1 (2)	(21)
Yee *et al*	2016	2 (5)	10 (26)	2 (5)	7 (18)	2 (5)	1 (3)	(28)

-, no data available.

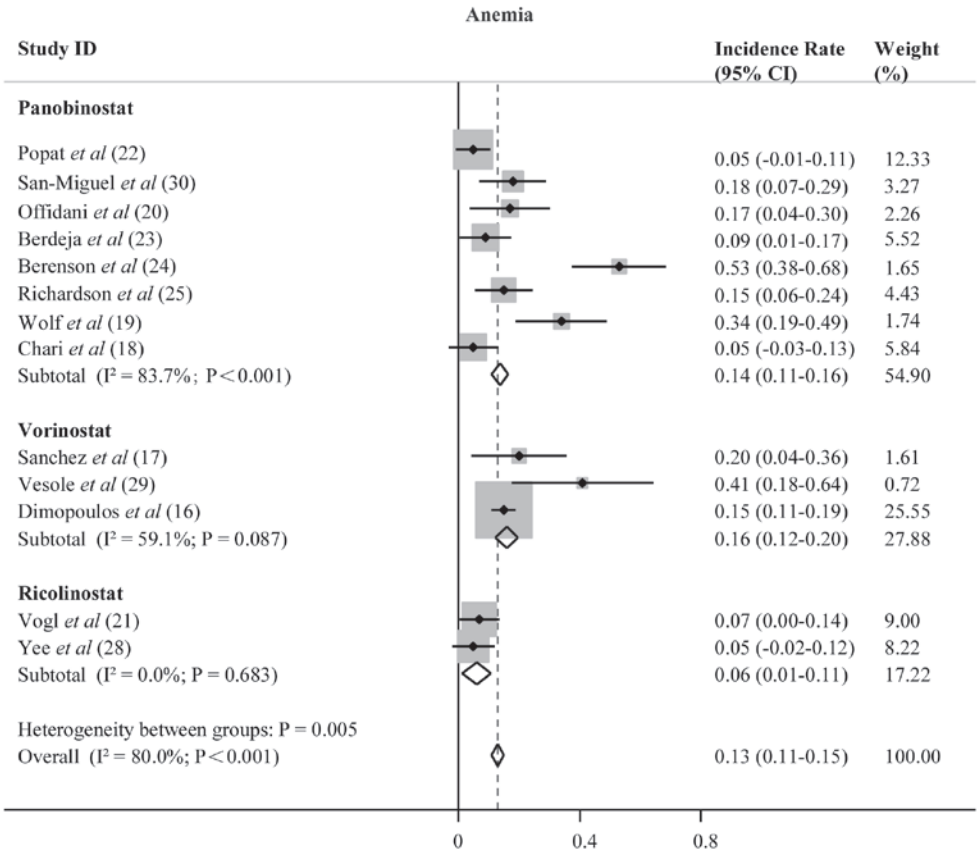

Figure 4. The incidence rate of grade 3 and 4 adverse event anemia. The vertical dashed line indicated overall incidence rate.

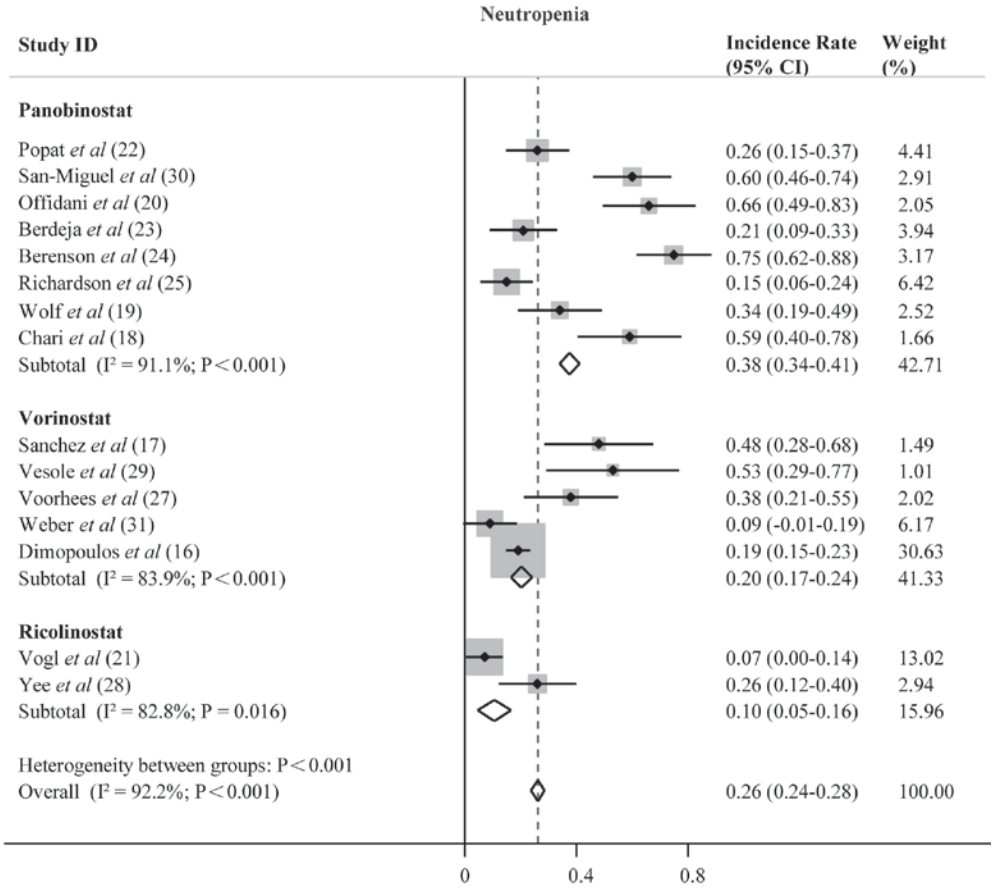

Figure 5. The incidence rate of grade 3 and 4 adverse event neutropenia. The vertical dashed line indicated overall incidence rate.

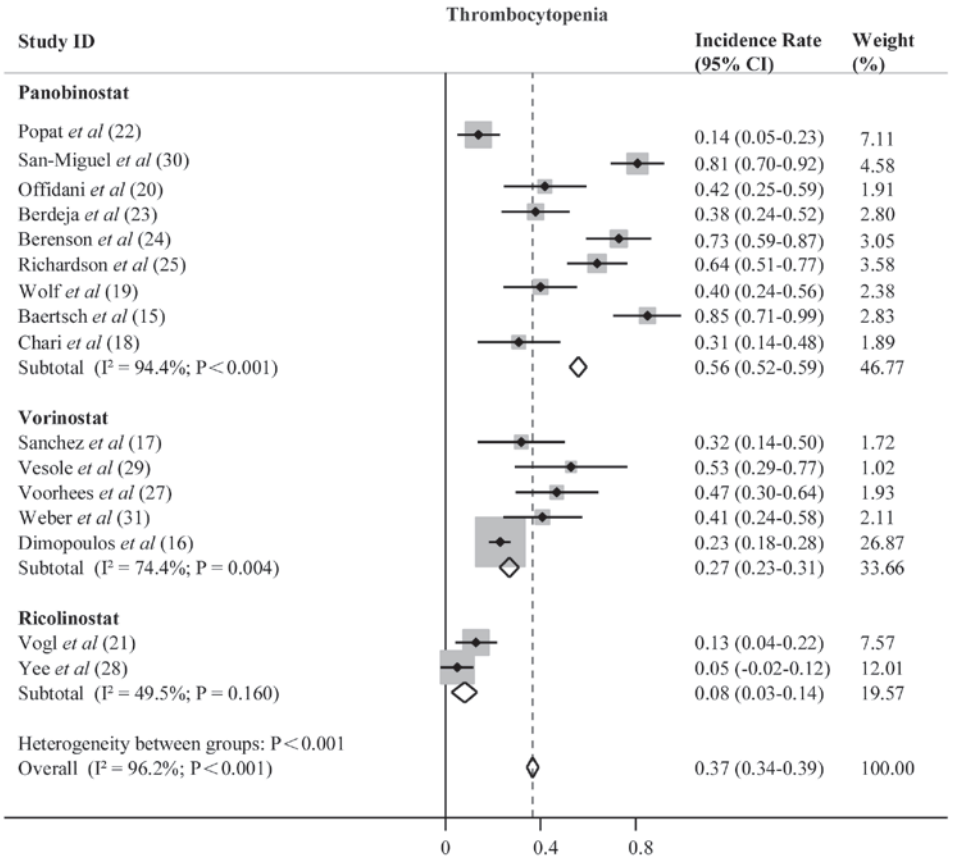

Figure 6. The incidence rate of grade 3 and 4 adverse event thrombocytopenia. The vertical dashed line indicated overall incidence rate.

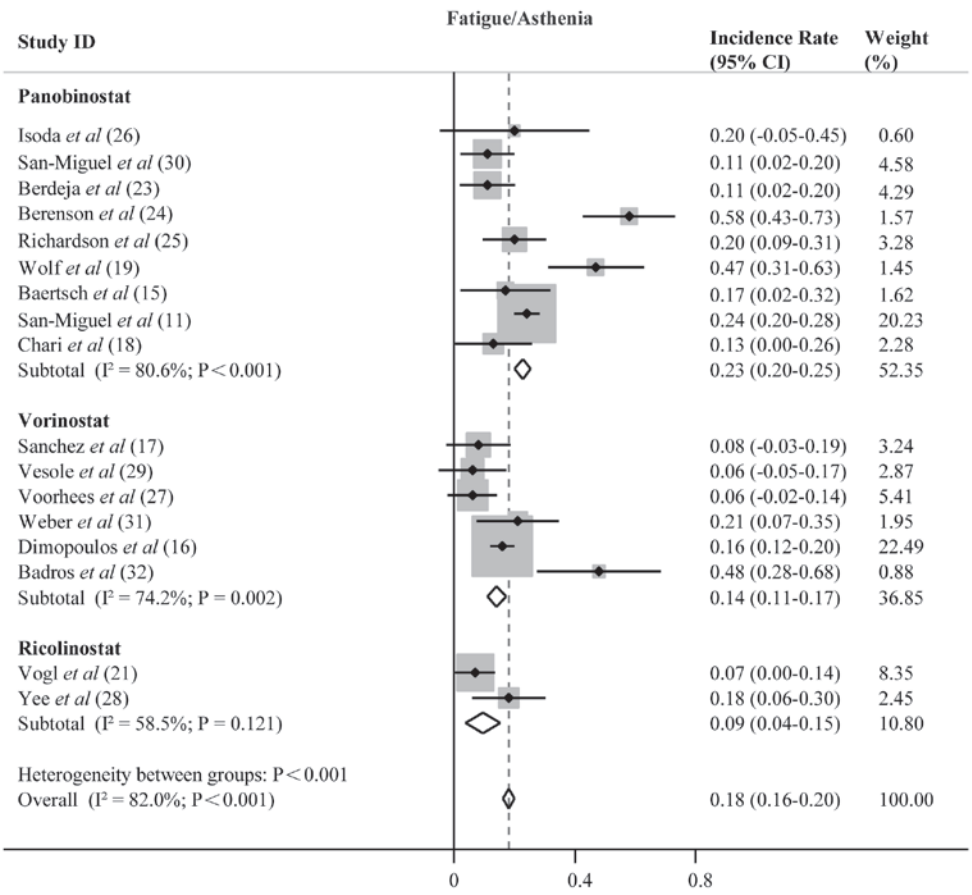

Figure 7. The incidence rate of grade 3 and 4 adverse event fatigue/asthenia. The vertical dashed line indicated overall incidence rate.

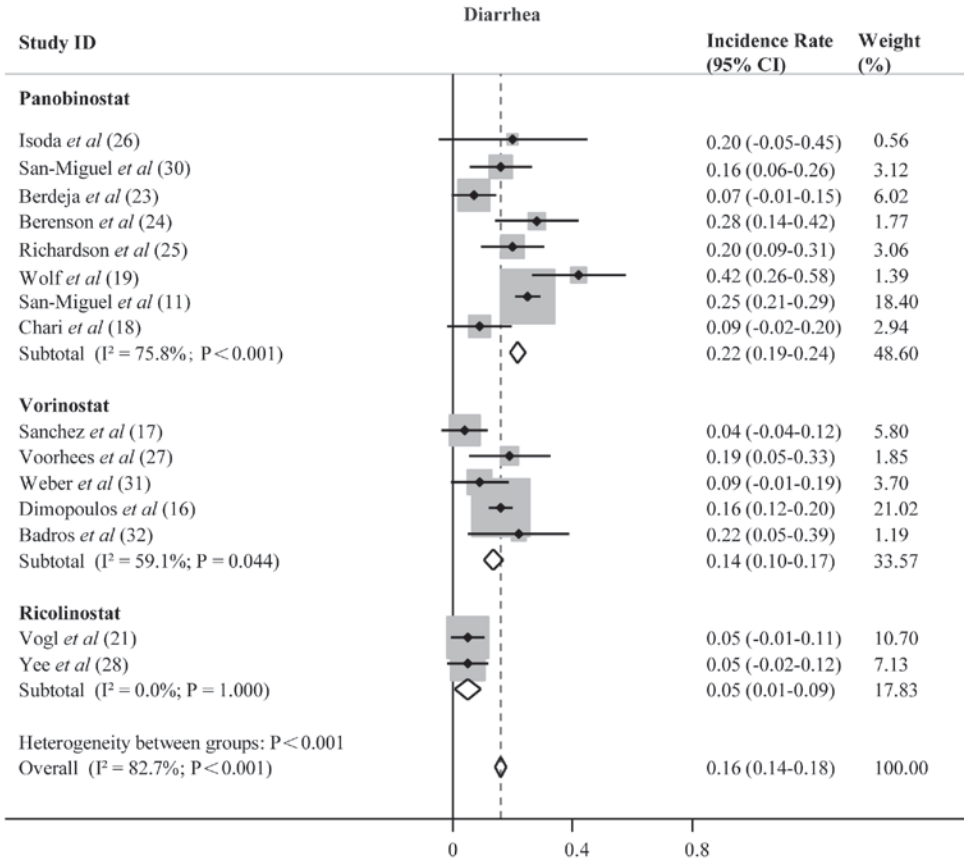

Figure 8. The incidence rate of grade 3 and 4 adverse event diarrhea. The vertical dashed line indicated overall incidence rate.

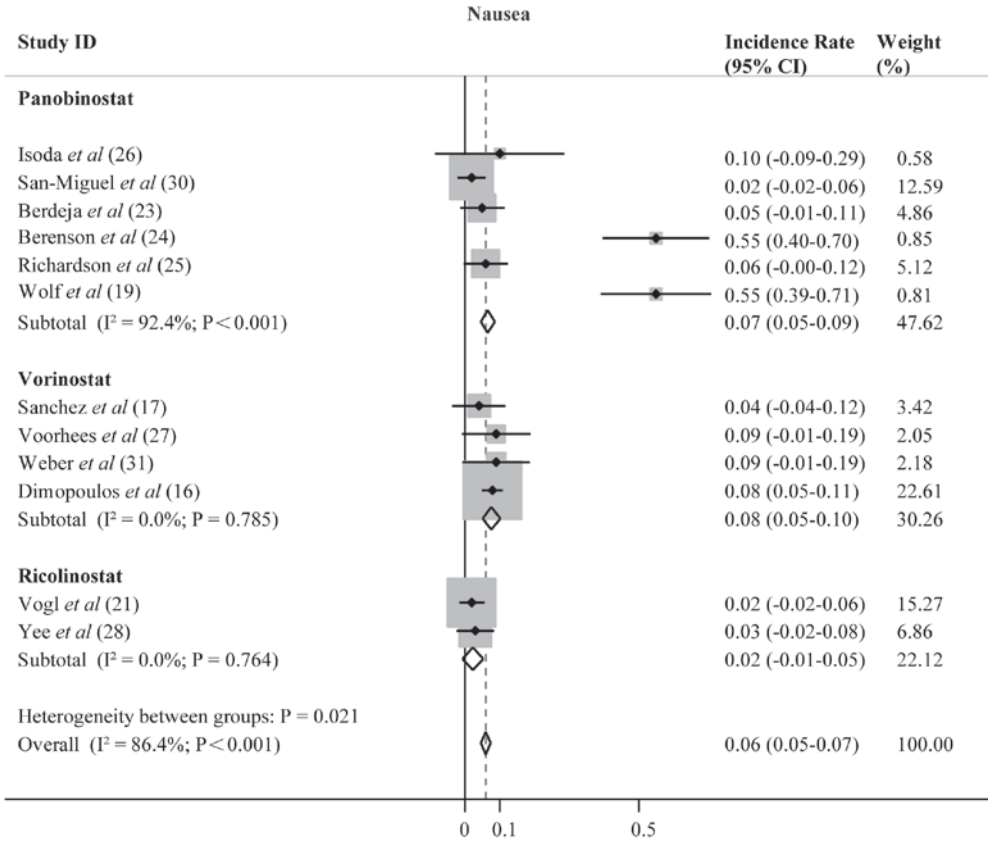

Figure 9. The incidence rate of grade 3 and 4 adverse event nausea. The vertical dashed line indicated overall incidence rate.

patients were treated in cohorts with doses of 40-240 mg. Although the MTD of ricolinostat was not established, a recommended phase II dose was defined at 160 mg (28). Overall, the data suggested that the doses used for the HDAC inhibitors varied based on different combination regimens.

The meta-analysis results indicated that panobinostat was more effective and safer than vorinostat and ricolinostat. In the subgroup analysis, the highest ORR of 0.64 was observed in RRMM patients treated with panobinostat. This was followed by ORRs of 0.51 and 0.38 in RRMM patients treated with vorinostat and ricolinostat, respectively. Panobinostat is a non-selective HDACi, targeting class I, II and IV HDACs. A study by Wolf *et al* (19) found that only one out of 38 patients achieved a partial response (PR) with panobinostat monotherapy. The outcome indicated that panobinostat alone showed little clinical efficacy in the treatment of RRMM. However, there was a significant improvement in clinical efficacy when panobinostat was used in combination with proteasome inhibitors (PIs) or immunomodulatory drugs (iMIDs) for RRMM. Importantly, a study by Popat *et al* (22) demonstrated that panobinostat in combination with bortezomib, thalidomide and dexamethasone generated an ORR of 0.91 (95% CI, 0.84-0.98), and lower rates of hematological adverse events, including neutropenia and thrombocytopenia in comparison to other studies. These results suggest that multidrug combinations may be more effective treatment strategies for RRMM. There were only a few studies with small sample sizes included in the ricolinostat-treated group for the pooled analysis (21,28). Ricolinostat, a selective inhibitor of HDAC6, preliminarily showed a weaker anti-MM effect than the other two drugs in the present study, thereby implying that selective HDACis are less effective than non selective HDACis (pan-HDACis).

In the present study, subgroup analysis also demonstrated that lenalidomide-refractory MM patients had a better ORR than bortezomib-refractory MM patients after treatment with HDACi-containing regimens. It was hypothesized that this may be due to PI-refractory patients not being responsive to HDAC inhibitors alone, but being responsive to the combined effect of PIs and HDACis.

In addition, the safety of the three drugs was evaluated by analyzing the incidence of adverse events. Panobinostat and vorinostat showed a similar trend of overall incidence of hematological adverse events of thrombocytopenia, neutropenia and anemia, and non-hematological adverse events of fatigue/asthenia, diarrhea and nausea. By contrast, the most common hematological adverse event for ricolinostat was neutropenia. The difference in adverse event profiles of HDAC inhibitors should be carefully considered by clinicians in the clinical management of patients with RRMM.

There were also several limitations in the present meta analyses which should be considered. First, in addition to 3 studies from Japan, Italy and Germany, the remaining 16 studies included in the current analysis were from the United States, suggesting that the outcome maybe be biased for the American population. Second, even with using a random effects model in statistical analysis, the data were still confounded by a high degree of heterogeneity. This was probably due to the numerous combination regimens administered in different studies. Third, most of the studies included in the

present analysis were single-arm clinical trials. There were only two phase III trials (11,16) that provided OS and PFS data, which are the main indicators used to evaluate drug efficacy in oncology clinical trials.

In conclusion, panobinostat-containing regimens were effective in treating patients with RRMM, but ricolinostat and vorinostat-containing regimens did not yield satisfactory results for patients with RRMM. Additionally, lenalidomide-refractory patients may benefit from HDACi treatment more than patients with bortezomib-refractory. However, a longer follow-up period is required to investigate crucial study endpoints of PFS and OS.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XG and LS directed the study and XG wrote the manuscript. XG and XL extracted data. JL conducted the statistical analysis of data. LS critically revised the article for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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