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2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0683 Vorinostat, Capsules Multiple Myeloma	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination With Bortezomib in Patients With Relapsed and Refractory Multiple Myeloma #095

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter; Seventy (70) study centers located in the Australia, Belgium, Canada, France, Germany, Greece, Israel, Italy, Spain, United Kingdom, United States, Russia, and South Korea participated in this study.

PUBLICATION(S):

Jagannath S, Siegel DS, Hajek R, Dimopoulos, Yoon S, Lonial S, et al [abstract]. J Clin Oncol. 2010;28:15(s),(suppl):Abstract 8133.

Siegel D, Jagannath S, Lonial S, Dimopoulos M, Graef T, Pietrangelo D, et al. [abstract]. Blood. 2009;114(22):Abstract 3890.

Siegel D, Jagannath S, Hajek R, Dimopoulos M, Yoon S, Lonial S, et al. [abstract]. Blood. 2010; 116 (21):Abstract 1952.

Siegel D, Jagannath S, Lonial S, Dimopoulos M, Yoon S, Graef T, et al. [abstract]. Haematologica. 2010; 95 (supplement no. 2): Abstract 0387.

Dimopoulos M, Siegel D, Jagannath S, Hajek R, Yoon S, Lonial S, et al. Presented at: 16th Congress of the European Hematology Association; 2011; Jun 9-12, London, United Kingdom.

PRIMARY THERAPY PERIOD: 06 Jan 2009 to 16 May 2011 | **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: Patients could continue to be treated until disease progression, unacceptable toxicity or the withdrawal of consent.

OBJECTIVE(S):

The primary objective was to define the objective response rate associated with the administration of vorinostat in combination with bortezomib to patients with relapsed and refractory multiple myeloma after at least 2 prior treatment regimens, who met both of the following conditions: a) Refractory to bortezomib (administered either alone or in combination with other agents); defined as no response on prior bortezomib-containing regimens or progression on or within 60 days of a bortezomib-containing regimen and b) Relapsed, refractory, intolerant, and/or ineligible (in the opinion of the Investigator) to other therapies, including an immunomodulatory drug (IMiD) (thalidomide OR lenalidomide).

The secondary objectives were: a) to assess the tolerability and adverse experience profile of vorinostat administered in combination with bortezomib, b) to assess the time to disease progression associated with the administration of vorinostat in combination with bortezomib, c) to evaluate the progression-free survival associated with the administration of vorinostat in combination with bortezomib, and d) to evaluate overall survival associated with the administration of vorinostat in combination with bortezomib.

STUDY DESIGN: This was a Phase IIb, international, multicenter, open-label, single arm study.

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CLINICAL STUDY REPORT SYNOPSIS

PATIENT DISPOSITION:

	Vorinostat + Bortezomib	
	n	**(%)**
ENROLLED:	143	
Male (age range 37-81)	87	(60.8)
Female (age range 42-77)	56	(39.2)
Number of Patients Treated	142	
DISCONTINUED:	137	(96.5)
Adverse event	28	(19.7)
Withdraw by subject	21	(14.8)
Protocol Violation	1	(0.7)
Lost to follow up	1	(0.7)
Physician decision	7	(4.9)
Progressive disease	79	(55.6)

DOSAGE/FORMULATION NOS.: Bortezomib injection, 1.3 mg/m² on Days 1, 4, 8, and 11, and oral capsules of vorinostat, 400 mg daily on Days 1-14 of each 21-day cycle. Patients with progressive disease after 2 cycles or no change after 4 cycles were permitted to add treatment with dexamethasone 20mg (oral tablets) on the day of and day after each dose of bortezomib.

Drug	**Potency**	[redacted]	**Dosage Form**	[redacted]
Vorinostat	100 mg		Capsules	
Bortezomib	3.5 mg		Powder for solution for injection	
Dexamethasone	4 mg		Tablets	

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MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. **CLINICAL STUDY REPORT SYNOPSIS**

DIAGNOSIS/INCLUSION CRITERIA: Patients with an established diagnosis of multiple myeloma with measurable myeloma disease were enrolled. Patients had to have relapsed and refractory multiple myeloma after at least 2 prior treatment regimens as per the EBMT response criteria and met both of the following conditions: Refractory to Bortezomib (administered either alone or in combination with other agents); defined as no response on prior bortezomib-containing regimens or progression on or within 60 days of a bortezomib-containing regimen and relapsed, refractory, intolerant, and/or ineligible (in the opinion of the Investigator) to other therapies, including an IMiD (thalidomide OR lenalidomide). Eligible patients must have been ≥ 18 years of age; had a performance status of ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale; adequate organ function; ability to swallow capsules; ≥ 3 weeks from prior chemotherapy, radiation therapy, biological therapy, immuno-therapy, major surgery or any other investigational anticancer therapy and have recovered from prior toxicities.

EVALUATION CRITERIA:

SAFETY MEASUREMENTS: Adverse experiences, laboratory safety assessments, Eastern Cooperative Oncology Group (ECOG) status, electrocardiogram (ECG)s, and vital signs were collected. Duration, intensity, and time to onset of toxicities were assessed.

EFFICACY MEASUREMENTS: In order to assess disease response, serum and urinary myeloma laboratory tests were to be collected every 21 days (± 2 days) following the first date of study drug (Cycle 1/Day 1) administration and sent to the central laboratory for analysis. Response to study therapy was assessed using European Blood and Marrow Transplantation Group (EBMT) criteria by an Independent Adjudication Committee (IAC).

STATISTICAL PLANNING AND ANALYSIS:

The primary endpoint for this study was response rate, defined as the percentage of subjects who achieved partial response or better during the study. Assuming a true response rate of 25% and accounting for the single futility analysis, 142 patients will provide 90% power to demonstrate a response rate >14%. With 142 patients enrolled, a response rate statistically > 14% corresponds to an observed response rate > 20%, an observed response rate that is considered clinically meaningful in this population.

Primary Efficacy Analyses

Objective Response Rate: The primary efficacy analysis was a test of the null hypothesis H_0: $p \leq 0.14$, where p was the proportion of patients who achieved a partial response or better on a regimen of vorinostat and bortezomib combined. The alternative hypothesis was H_A: $p > 0.14$. An exact analysis on a single binomial parameter was used to test the null hypothesis. An exact 95% confidence interval for the true proportion of patients responding to the combined treatment regimen was also provided.

Secondary Efficacy Analyses

Time to Progression: Since disease progression was assessed periodically, the true date of disease progression was known only to occur at a time point after the last assessment of No Change (or better) and prior to the date of the assessment of progression. For the primary and supportive analyses, for patients with disease progression, the true date of disease progression was approximated by the date of the first myeloma assessment at which disease progression was documented. A non-parametric Kaplan-Meier method was used to estimate the TTP curve and the median TTP for treated patients.

Progression-free Survival: The methods that were used for the analysis of PFS are the same as those that were used for TTP.

Overall Survival: The non-parametric Kaplan-Meier method was used to estimate the survival time distribution and the median survival of the treated patients. In the overall survival analysis, patients

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were censored only if they discontinued from all study follow-up periods with no prior record of death and without any further follow-up for death.

Safety Analysis: Safety and tolerability were assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, and ECG measurements. Additional safety analyses: time to the first occurrence of a Grade 3-5 AE were estimated using Kaplan-Meier methods.

RESULTS:

Efficacy

Of the 142 patients who received at least one dose of study treatment, 16 patients had a Partial Response (PR) or better during the study according to EBMT criteria, for an objective response rate of 11.3%. The median time to response was 44 days and the median duration of response was 211 days. The study protocol allowed for dexamethasone use in patients who experienced disease progression after 2 cycles of treatment or no change after 4 cycles of treatment; however, for the primary response assessment patients were censored when dexamethasone was added to study therapy. The statistical criterion for success of this study required an objective response rate that is statistically significantly greater than 14%. The two-sided p-value was 0.419 for the comparison of the objective response rate with 14%. The study failed to meet the protocol-specified success criterion for the primary hypothesis.

Response was further assessed using the revised International Myeloma Working Group (IMWG) criteria and not censoring for dexamethasone treatment; the objective response rate was 16.9%. Another indicator of response is the clinical benefit rate (CBR) which reports minimal response (MR) or better. The CBR using IMWG criteria and not censoring for dexamethasone was 31.0% with a median duration of response 192 days.

The observed median overall survival (OS) in this study was 11.23 months. In the Kaplan-Meier plot for OS, there is a suggestion of a plateau at one year. The 2 year survival rate was 39%.

Safety

Clinical adverse experiences were reported in all patients enrolled in this study, and 131 (92.3%) patients had adverse experiences that were considered by the Investigator to be related to the study medication. Serious drug related clinical adverse experiences were reported in 29 (20.4%) patients. A total of 24 (16.9%) patients died on study, of which 18 reported an AE of neoplasm malignant, (ie, disease progression). One (1) died due to a drug-related clinical event of a cerebral haemorrhage triggered by a thrombocytopenia Grade 4 event).

The 5 most frequently-reported adverse events were thrombocytopenia (69.7%; 68.3% ≥ Grade 3), nausea (57.0%; 7.0% ≥ Grade 3), diarrhoea (53.5%, 16.9% ≥ Grade 3), anaemia (52.1%, 38.0% ≥ Grade 3) and fatigue (48.6%, 13.4% ≥ Grade 3). A total of 27 patients discontinued the study due to a treatment emergent AE. The most common AEs of any grade that led to discontinuation included diarrhoea, asthenia, thrombocytopenia, pneumonia, and neuralgia.

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CONCLUSIONS:

Efficacy Conclusions

- The statistical criterion for success of this study (objective response rate [EBMT]) that is statistically significantly greater than 14%) was not met.
- Per IMWG response criteria, the combination of bortezomib and vorinostat demonstrated some clinical activity based on an observed overall response of 16.9% and a clinical benefit response rate of 31.0% with a median duration of 192 days.
- The median OS in this particular patient population was 11.23 months with a 2-year OS rate of 32%. However, the OS data set at the time of database cutoff was not considered mature enough to draw a final conclusion.

Safety Conclusions

- The nature and overall frequency of adverse events observed in this study were similar to those observed in other studies of vorinostat and bortezomib monotherapy.
- The increased frequency of observed Grade 4 thrombocytopenia (52.8%) did not result in increased reports of bleeding associated events and were manageable through supportive care and appropriate dose modifications.
- In the absence of early disease progression patients tolerated the study treatment up to mean of 6.2 cycles (range: 1 – 26 cycles).

AUTHORS:	(Writer)	(Statistician)	(Clin. Monitor)
	[redacted]		

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