Sponsor Company Name: Millennium Pharmaceuticals, Inc.

Name of Finished Product: VELCADE (bortezomib) for Injection

Name of Active Ingredient: bortezomib

Study Title: A Multicenter, Open-label, Phase 2 Study of VELCADE (bortezomib) for Injection in Previously Treated Patients with Stage IIIB and IV Bronchioloalveolar Carcinoma and Adenocarcinoma with Bronchioloalveolar Features

Investigator(s): [redacted]

Study Center(s): A total of 35 clinical sites (29 United States, 3 France, 2 The Netherlands, 1 United Kingdom)

Publication (reference): Not applicable

Study Phase: 2

Study Period:

Initiation Date (first subject enrolled): 13 April 2005

Early Termination Date: 25 September 2006 (terminated due to insufficient efficacy)

Completion Date (last subject completed): 8 June 2007 (last clinic visit except for 1 ongoing patient. As of 19 May 2008, this patient remained on study treatment.)

STUDY OBJECTIVES:

Primary: To determine the efficacy of VELCADE in terms of tumor response rate (complete response [CR] and partial response [PR]) using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria[(1)] in patients with advanced bronchioloalveolar carcinoma (BAC) or adenocarcinoma with BAC features that have progressed on or after Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKI).

Secondary:

- To determine the duration of response, disease control rate, time to progression (TTP), and survival following VELCADE therapy
- To assess the toxicity and tolerability of VELCADE therapy
- To correlate somatic mutations in v-Ki-ras2 Kirsten rat sarcoma (KRAS) and EGFR genes with response to VELCADE therapy

- To explore the association between somatic mutations and expression levels in genes that may be involved in BAC prognosis or response to VELCADE therapy (p53, cyclin D1, Ki-67, p21cip1, p27kipl, thyroid transcription factor-1 [TTF-1], osteopontin, proteasome subunits)
- To assess patient reported outcomes (PROs) using quality of life (QOL) instruments (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC-QLQ-C30] with its lung cancer module QLQ-LC13, and the Lung Cancer Symptom Scale [LCSS])
- To assess the medical resource utilization (MRU) related to the disease and the therapy

METHODOLOGY:

This was a multicenter, open-label, phase 2 study designed mainly to determine the efficacy of VELCADE therapy as measured by the objective tumor response rate (CR and PR as assessed using the RECIST criteria) in patients with advanced BAC or adenocarcinoma with BAC features who had progressed on or after EGFR TKI therapy.

After providing written, informed consent to participate in the study, patients were evaluated for study eligibility during a Screening visit within 14 days before the first dose on Cycle 1, Day 1. Eligible patients were treated with 1.5 mg/m^2 VELCADE administered twice weekly on Days 1, 4, 8, and 11 of a 21-day cycle. Consenting patients also were asked to provide blood samples for exploratory pharmacogenomic studies to be conducted by Millennium Pharmaceuticals, Inc. (Millennium), and to complete QOL and MRU questionnaires.

Patients were evaluated by the investigator for tumor response (CR and PR) using the RECIST criteria, based on CT or MRI scans obtained every 2 cycles (6 weeks). Treatment cycles were repeated every 21 days until the patient achieved progressive disease (PD), CR, or experienced an unacceptable adverse event (AE), death, or another criterion for withdrawal. Patients who achieved CR were to be treated for up to 2 cycles beyond confirmation of CR.

Patients who completed the study with CR were followed every 6 weeks for disease assessment. If a patient completed the study or withdrew from treatment before PD was documented, they continued to have disease assessments every 6 weeks until PD was documented or they received another antineoplastic therapy. All patients were followed for survival every 3 months from time of PD or treatment with another antineoplastic therapy through the end of study. The end of study was defined as 6 months after the last dose was administered to the last patient on study, at which time no further patient assessments took place. (Note: The end of study was actually 6 months after the last dose was administered to the second-to-last patient on study; 1 patient was receiving study treatment at the time of final analyses.)

Number of Subjects (planned and analyzed): Approximately 150 patients were to be enrolled and treated in this study (assuming at least 90% of patients would be evaluable for response). A total of 69 patients were enrolled in the study at the time of study termination. The sponsor terminated the study because the results from the second interim analysis did not demonstrate sufficient efficacy to continue.

Diagnosis and Main Criteria for Inclusion: Male and female patients with advanced [stage IIIB with malignant pleural effusion or stage IV] adenocarcinoma of the lung classified as pure BAC or adenocarcinoma with BAC features, who had progressed on or after treatment with an EGFR TKI (Iressa® [gefitinib] or Tarceva™ [erlotinib]). Additionally, patients must have had microscopic slides or archived tissue for histological confirmation of the diagnosis of BAC or adenocarcinoma with BAC features.

Test Product, Dose, and Mode of Administration: VELCADE 1.5 mg/m^2, was administered twice weekly on Days 1, 4, 8, and 11 of a 21-day cycle by a 3- to 5-second intravenous (IV) push.

Duration of Treatment: Patients remained on treatment until PD, CR, the occurrence of an unacceptable AE, death, or until any other criterion for withdrawal from treatment was met. In the case of CR, treatment continued for up to 2 cycles beyond the date of confirmation of CR.

CRITERIA FOR EVALUATION:

Efficacy Assessments: The primary endpoint was the efficacy of VELCADE therapy as measured by objective tumor response rate (CR and PR).

Secondary efficacy endpoints evaluated were disease control rate; TTP; survival (progression-free survival [PFS], 12-month survival, and overall survival); and potential association between somatic mutations in KRAS and EGFR and tumor response to VELCADE. Other efficacy endpoints included disease-related symptom relief as assessed by the EORTC QOL instrument (EORTC-QLQ-C30 with its lung cancer module QLQ-LC13) and LCSS.

Pharmacogenetic Assessments: Tumor samples were obtained from 47/69 patients (68%). DNA was prepared from either 100-micron sections of whole blocks or from tissue scraped off and pooled from 2 to 3 glass slides. Mutation profiling for KRAS mutations was performed using polymerase chain reaction/ligase detection reaction (PCR / LDR). The following mutations were targeted for detection in multiplex: p.G12V, p.G12S, p.G12D, p.G12R, p.G12A, p.G12C, p.G13D. Forty-five of 47 tumor samples were evaluable for KRAS mutations. EGFR mutation detection was performed using PCR/LDR to detect 14 point mutations using the method described above, as well as 2 insertion/deletion mutations using the capillary electrophoresis methodology. Detection was performed in multiplex and the following mutations were targeted: p.E709K, p.E709G, p.G719S, p.G719C, p.G719A, p.S720F, p.S768I, p.G779F, p.T790M, p.L792P, p.N826S, p.L858R (NM_005228:c.2573 T>G), p.L858R (NM_005228:c.2573-2574 TG>GT), p.L861Q, p.E746_A750del ((NM_005228:c. 2235_2249del) and p.E746_A750del (NM_005228:c.2236_2250del). To capture insertion/deletion mutations that were of lower frequency than those cited above, fluorescent PCR was performed using primers that flanked the region in exon 19 that is a hotspot for insertion/deletions. Forty-five of 47 DNA samples were evaluable for EGFR mutations.

Safety Assessments: The safety assessment was based on AE monitoring, physical examinations, vital signs, and clinical laboratory evaluations.

Statistical Methods: The primary efficacy analysis was on the objective tumor response rate (combined CR and PR). An estimate of the response rate was presented with a 2-sided 95% confidence interval. The number and percentage of patients falling into each response category (CR, PR, stable disease [SD], and PD) was descriptively tabulated.

TTP, PFS, and 12-month and overall survival were analyzed using standard survival analysis techniques such as Kaplan-Meier test methods. Disease control rate (combined rate of objective CR, PR, and SD) was analyzed similarly to the primary endpoint.

Two genes were tested for potential association with response to VELCADE: KRAS and EGFR.

AE incidence was tabulated for the following categories: all AEs; most common (≥10%) AEs; drug-related events; severe (Grade 3 or worse) AEs; drug-related and severe (Grade 3 or worse) AEs; deaths; serious adverse events (SAEs); and AEs resulting in discontinuation of VELCADE. For laboratory parameters, shift tables were produced to tabulate changes from baseline Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade to post-baseline worst CTCAE grade. Actual values and changes from baseline in weight and body surface area were descriptively summarized over time.

Three interim analyses were to be conducted after the first 25, 50, and 85 response-evaluable patients had the opportunity to complete up to 4 cycles of therapy. If there were at least 1, 3, and 7 responders out of these 25, 50, and 85 response-evaluable patients in each stage, respectively, the study was to continue. Otherwise, the study was to be discontinued for futility. Two interim analyses were performed, on 28 March 2006 and 5 September 2006, and the study was terminated based on the results of the second interim analysis. Of the first 50 response-evaluable patients, the population used for the second interim analysis, there was 1 confirmed PR per RECIST criteria. Therefore, the study was unable to meet the interim analysis criterion of 3 confirmed partial responses for continuation of the study.

RESULTS AND CONCLUSIONS

Because the results from the second interim analysis of this study did not demonstrate sufficient efficacy, the study was terminated, as per the protocol. Full safety evaluations were conducted; however, only select efficacy data were analyzed. In addition, analyses were not performed to explore the association between somatic mutations and expression levels in genes that may be involved in BAC prognosis or response to VELCADE therapy (p53, cyclin D1, Ki 67, p21cip1, p27kipl, TTF-1, osteopontin, proteasome subunits). PRO and MRU data were not summarized.

Demographic and Baseline Characteristics: A total of 69 patients were enrolled in this study and received study drug. These 69 patients comprise the Safety Population. Of the 69 patients in the Safety Population, 56 (81%) patients were included in the Response-Evaluable Population, which was used for the primary efficacy analysis.

Of the 69 treated patients, 68 (99%) patients discontinued study treatment; one patient was ongoing at the time of final analyses. The most frequent reason for discontinuation of study treatment was progressive disease (57%). A total of 10 (14%) patients discontinued study treatment because of an AE. The majority of patients were female (61%), and most (90%) were white. Mean age was 62 years, ranging from 22 to 83 years. The majority of patients (72%) had a history of smoking; these patients had smoked an average of 25 years. Most patients (91%) had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

In keeping with the inclusion criteria for this study, all patients had stage IIIB disease with malignant pleural effusion (n = 2, 3%) or stage IV disease (n = 67, 97%).

All patients in this study had received at least 1 line of prior antineoplastic therapy for advanced BAC. The mean number of lines received was 2.2 (range of 1–7). Most patients (87%) had received prior antineoplastic therapy within 3 months of their first dose of VELCADE. Best response to prior antineoplastic therapy was SD (49%) or PD (26%) in the majority of patients; only 7% and 16% had achieved CR or PR, respectively.

Efficacy Results:

Primary Efficacy Endpoint: The primary efficacy endpoint in this study was objective tumor response rate (CR + PR) using the RECIST criteria.

The response rate (CR + PR) was 4% (2 of 56 patients) (95% confidence interval [CI]: 0, 12); both patients achieved a PR. The disease control rate (CR + PR + SD), which was a secondary endpoint in this study, was 48% (27 of 56 patients) (95% CI: 35, 62).

Investigator Assessment of Best Response to Treatment (Response-Evaluable Population, N = 56)

Response Category	VELCADE 1.5 mg/m^2 (N = 56) n (%) [95% CI]
Response Rate (CR + PR)	2 (4) [0, 12]
Disease Control Rate (CR + PR + SD)	27 (48) [35, 62]
Complete Response (CR)	0
Partial Response (PR)	2 (4) [0, 12]
Stable Disease (SD)	25 (45) [31, 59]
Progressive Disease (PD)	22 (39) [26, 53]
No Post-Baseline Assessment	7 (13) [5, 24]

CI = confidence interval

Secondary Efficacy Endpoints:

Overall Survival: Of the 69 treated patients, 26 (38%) died. The Kaplan-Meier estimate of median overall survival was ~18.6 months (566 days; 95% CI: 387, 644). The Kaplan-Meier estimate of probability of survival at 1 year was 67%. The median duration of follow-up for surviving patients was ~1 year (374 days).

Progression Free Survival: Of the 69 patients, 58 (85%) died or experienced disease progression. The Kaplan-Meier estimate of median PFS was 52 days (95% CI: 39, 91).

Pharmacogenetic Results: KRAS mutations were observed in 19 of the 45 (42%) evaluable DNA samples and EGFR mutations were observed in 28 of the 45 (62%) evaluable samples. No significant differences were observed in any of the variables of response rate, TTP, or PFS between KRAS mutant and wild type tumors or EGFR mutant and wild type tumors. DNA was available for KRAS and EGFR analysis on one of two patients enrolled in the study who had a PR. As assessed in the safety population, there was 1 PR out of 24 patients with wild type KRAS (4%) and 0 PR out of 17 patients with KRAS mutations. There was 1 objective response out of 25 patients with EGFR mutations (4%) and 0 objective responses out of 16 patients with wild type EGFR.

Safety Results: All patients experienced at least 1 treatment-emergent AE (100%), and most (96%) experienced at least 1 AE related to VELCADE. The most common treatment-emergent AEs (regardless of drug attribution) were fatigue (62%), nausea (61%), peripheral neuropathy (48%), constipation (46%), and diarrhea (45%).

The majority (70%) of patients had a Grade 3 or worse AE, and half (51%) had a Grade 3 or worse, drug-related AE. The most common Grade 3 or worse, drug-related AEs were fatigue (14%), thrombocytopenia (9%), diarrhea (7%), nausea (6%), and peripheral neuropathy (6%).

Six (9%) patients died on treatment (within 30 days after last dose), and 1 death was considered related to VELCADE. In this case, the patient died of pneumonia, sepsis, and cardio-pulmonary arrest. In the opinion of the investigator, life-threatening immunodeficiency attributed to use of VELCADE may have contributed to the patient developing these conditions. Thus, the investigator reported each event (pneumonia, sepsis, cardio-pulmonary arrest, and immunodeficiency) as related to VELCADE.

A total of 24 (35%) patients experienced an SAE, and 11 (16%) patients had a drug-related SAE. Drug-related SAEs that occurred in >1 patient were pyrexia, pneumonia, and diarrhea (2 patients each). There were no cases of serious peripheral neuropathy (regardless of drug attribution).

Fourteen (20%) patients discontinued VELCADE due to an AE. The only event that resulted in discontinuation in >1 patient was peripheral neuropathy (n = 7, 10%).

Few patients had a treatment-emergent CTC Grade 3 or Grade 4 hematology or clinical chemistry abnormality. Two (3%) patients had a laboratory abnormality reported as a drug-related SAE (thrombocytopenia or platelet count decreased). Both patients had normal platelet counts at baseline.

Four (6%) patients had an abnormality in vital signs reported as a drug-related SAE. These events were pyrexia (2 patients), orthostatic hypotension (1 patient), and postural hypotension (1 patient).

CONCLUSIONS

The degree of efficacy seen in this study does not support additional study of VELCADE as a single agent in BAC or adenocarcinoma with BAC features. The safety profile is consistent with that seen in multiple myeloma and mantle cell lymphoma.[(2)]

Tumor KRAS and EGFR mutations were not associated with a statistically different overall response rate, median TTP and PFS versus KRAS and EGFR wild type tumors.

Date of Synopsis: 29 May 2008

REFERENCES:

1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92 (3):205-16.
2. VELCADE® (bortezomib) for Injection, October [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2007.

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