PATIENTS AND METHODS

Patients

Patients aged 18 years or older with measurable secretory MM (serum monoclonal protein ≥1 g/dL or urine M-protein ≥200 mg/24 hours) who had relapsed/progressed following, or who were refractory to, one previous line of therapy were eligible. Patients were required to have a Karnofsky Performance Status of ≥60%, a life expectancy ≥6 months, and adequate hematologic and hepatic function, defined as: platelets ≥50 x 10^9/L, hemoglobin ≥7.5 g/dL, absolute neutrophil count ≥0.75 x 10^9/L, corrected serum calcium <14 mg/dL, aspartate/alanine aminotransferase ≤2.5 times upper limit of normal, and total bilirubin ≤1.5 times upper limit of normal. There were no eligibility restrictions based on renal function. Patients were excluded if they had: received nitrosoureas or any other chemotherapy (including thalidomide), clarithromycin, or interferon within 6 weeks, or undergone major surgery within 4 weeks of the start of the study; grade ≥2 peripheral neuropathy or neuropathic pain as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; received corticosteroids (>10 mg/day prednisone or equivalent) within 3 weeks, immunotherapy/antibody therapy within 8 weeks, plasmapheresis within 2 weeks, or an experimental drug/device within 4 weeks before enrollment; myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

All patients provided written informed consent. Review boards at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice.

Study design

This was a randomized, open-label, parallel-group, phase 2 study conducted at 49 sites in 10 European countries (France, Germany, Greece, Hungary, Lithuania, Poland, Serbia, Spain, Turkey, and the United Kingdom) from 12 May 2008–2 Aug 2011 (enrollment from 5 May 2008 to 31 December 2009), and is registered with ClinicalTrials.gov (NCT00908232), and EudraCT (2007-001462-33). The study design is shown in Figure 1. All patients were initially to receive four 21-day cycles of bortezomib-dexamethasone, which comprised bortezomib 1.3 mg/m^2 IV bolus on days 1, 4, 8, and 11, and dexamethasone 20 mg p.o. daily on the days of and after bortezomib dosing (days 1, 2, 4, 5, 8, 9, 11, and 12).

Subsequent treatment was dependent on patients' investigator-assessed response at the end of cycle 4 (cycle 5, day 1). Patients achieving at least partial response (PR) received a further four cycles of bortezomib-dexamethasone. Patients with SD were randomized (1:1:1), for cycles 5–8, to either: a further four cycles of bortezomib-dexamethasone, four cycles of bortezomib-dexamethasone as above plus cyclophosphamide 500 mg p.o. daily on days 1, 8, and 15 (VDC), or four cycles of bortezomib-dexamethasone as above plus lenalidomide 10 mg p.o. daily on days 1–14 (VDR). Randomization was based upon a computer-generated randomization schedule prepared prior to the study by the sponsor, and was stratified by age (<65 vs. ≥65 years) and country. Patients with progressive disease (PD) during or after the initial four cycles of bortezomib-dexamethasone discontinued study treatment.

All patients allocated to VDR who had any risk factor for venous thromboembolism were to receive concomitant prophylactic therapy of aspirin 81–100 mg p.o. daily or low-dose low

molecular weight heparin (LMWH). Additionally, supportive therapies were permitted, including GCSF/GM-CSF, erythropoietins, and bisphosphonates, as required. Concomitant corticosteroids (other than dexamethasone as part of study treatment), anti-neoplastic agents with anti-MM activity, radiation therapy, and investigational agents for MM were not permitted. Subsequent anti-MM therapy following completion of study treatment was not permitted until PD was established.

Assessments

The primary objective was to assess the response rate to continued bortezomib-dexamethasone, VDC, or VDR in patients who achieved SD after four cycles of bortezomib-dexamethasone. The secondary objectives consisted of other efficacy parameters, including time to response, duration of response (DOR), time to progression (TTP), progression-free survival (PFS), 1-year survival rate and overall survival (OS); assessment of the safety profile; and evaluation of change in renal function after four initial cycles of bortezomib-dexamethasone. Due to the majority of patients receiving bortezomib-dexamethasone for all eight planned treatment cycles, changes in renal function were assessed from baseline through cycle 8. Other assessments included safety and efficacy at the end of bortezomib-dexamethasone treatment (8 cycles) and at the end of the 1-year follow-up period.

Response was assessed using the International Myeloma Working Group (IMWG) uniform response criteria.[22] Assessments were based on serum and urine M-protein levels, which were evaluated at baseline, prior to treatment on day 1 of each cycle, at the end-of-treatment visit, and monthly thereafter. Response assessment was validated by an Independent Data Monitoring Committee (IDMC). Patients were followed monthly until progression/relapse and then every other month for survival, until the last enrolled patient had been followed for 1 year. Safety was monitored throughout the study and until 30 days after the last dose of

study drug. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Bortezomib dose modifications for peripheral neuropathy (PN) AEs were recommended per established guidelines.[23]

Renal function was defined by calculated glomerular filtration rate (GFR) using the Cockcroft-Gault formula[23] and was divided into the following stages by GFR based on the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative:[24] Stage I/II, ≥60 mL/min; Stage III, 30–<60 mL/min; Stage IV, 15–<30 mL/min; Stage V, <15 mL/min. GFR was assessed at baseline or screening, prior to treatment on day 1 of each cycle, and at the end-of-treatment visit. Patients were assessed for renal function stage migration between baseline and best on-study GFR. Additionally, patients were evaluated for renal response, based upon baseline and best on-study GFR, according to previously reported criteria.[25] A renal complete response (CR^{renal}) was defined as a GFR improvement from <15, 15–<30, or 30–<50 mL/min at baseline to ≥60 mL/min; a renal partial response (PR^{renal}) as an improvement from <15 to 30–<60 mL/min, with a >100% GFR increase; and a renal minor response (MR^{renal}) as an improvement from <15 to 15–<30 mL/min or from 15–<30 to 30–<60 mL/min, with a >50% GFR increase.

Statistical Methods

A sample size of 190 patients was determined for the study, based on the assumption that approximately 60% of patients would have SD after four cycles of bortezomib-dexamethasone and the intention to enroll approximately 38 patients per randomized treatment arm. The modified intention-to-treat (mITT) population comprised all patients who received at least one dose of study drug and who had at least one post-baseline efficacy assessment, and was used for analyses of safety and outcomes (TTP, PFS, OS). Time-to-event distributions were estimated using the Kaplan-Meier method. Overall best confirmed

response to treatment was assessed in all patients in the mITT population with IDMC-validated best confirmed response data. However, as noted, investigator-assessed response was used when determining entry into the randomized sequential therapy portion of the study. Changes in renal function were evaluated in all patients in the mITT population who had baseline and on-study assessments of GFR.