Study Number: C18770/2043
Title: An Open-Label Study to Determine the Maximum Tolerated Dose and Evaluate the Efficacy and Safety of CEP-18770 in Patients With Relapsed Multiple Myeloma Refractory to the Most Recent Therapy
Phase: Phase 1/Phase 2
Study Centers: The study was conducted at 27 centers in Belgium, France, Spain, and the United States of America (USA).
Study Initiation Date (first patient enrolled): 04 January 2010 **Study Completion Date (last patient completed):** 14 November 2012 **Report Approval Date:** 31 October 2013

Objectives: The primary objective for part 1 of the study was to determine the maximum tolerated dose (MTD) of CEP-18770 administered intravenously on days 1, 8, and 15 of a 28-day cycle in patients with relapsed multiple myeloma refractory to their most recent therapy.

The primary objective for part 2 of the study was to evaluate the antitumor activity of CEP-18770 in patients treated at the MTD (2.1 mg/m^2) on this schedule, including patients treated at the MTD (2.1 mg/m^2) in part 1. The antitumor activity was assessed by overall response rate (ORR) including stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), according to the International Myeloma Working Group criteria.

The secondary objectives of the study were as follows:

- to evaluate the durability of response as determined by duration of response (DOR) to CEP-18770 (part 2 and patients treated at the MTD [2.1 mg/m^2] in part 1)
- to determine the time to response (TTR) to CEP-18770 (part 2 and patients treated at the MTD (2.1 mg/m^2) in part 1)
- to assess the time to progression (TTP) with CEP-18770 (part 2 and patients treated at the MTD [2.1 mg/m^2] in part 1)
- to further characterize the pharmacokinetics of CEP-18770 on days 1, 8, and 15 of a 28-day cycle
- to assess the exposure/response relationship of CEP-18770 and to assess whether there is a relationship between systemic exposure and relevant safety parameters
- to evaluate proteasome inhibition by CEP-18770
- to evaluate the safety of treatment with CEP-18770 administered intravenously on days 1, 8, and 15 of a 28-day cycle to patients with relapsed and refractory multiple myeloma, as assessed by the following:
  - occurrence of adverse events throughout the study
  - clinical laboratory (serum chemistry, hematology, urinalysis, and coagulation profile) test results at specified time points throughout the study
  - vital signs (blood pressure and pulse) measurements at each visit
  - electrocardiograms (ECGs) in triplicate at specified time points prior to and after study drug administration
  - physical examination findings, including body weight measurements, at specified time points throughout the study
  - Eastern Cooperative Oncology Group (ECOG) performance status at specified time points throughout the study
  - concomitant medication usage throughout the study

Study Design and Duration: This was a Phase 1/Phase 2, multicenter, open-label, nonrandomized study in patients with relapsed multiple myeloma refractory to the most recent therapy.

Part 1 of the study determined the MTD and dose-limiting toxicities (DLTs) of CEP-18770 administered on days 1, 8, and 15 of a 28-day cycle in this patient population. Part 2 of the study evaluated the efficacy and safety of intravenous CEP-18770 treatment.

Part 1 of the study followed a dose-escalation design with patients recruited in cohorts of 3 (with criteria to expand to 6 patients). The MTD was based on the assessment of DLT during cycle 1 only, and was defined as the highest dose at which fewer than one-third of patients in a cohort experienced DLT to CEP-18770.

Screening occurred within the 14 days before the start of treatment with study drug, after the patient provided informed consent. Inclusion and exclusion criteria were assessed. Screening assessments and procedures included medical history and demographic information; cancer history and cancer treatment history; prior medication inquiry; physical examination including skin examination and limited neurologic (motor, reflexes, and sensory) examination; vital signs measurements; ECOG performance status; computed tomography (CT) scan or magnetic resonance imaging (MRI) for patients with soft tissue plasmacytoma or when clinically indicated; 12-lead ECG; serum chemistry, hematology, coagulation, and urinalysis testing; serum pregnancy test for women of childbearing potential; serum protein electrophoresis (SPEP) with immunofixation; 24-hour urine protein electrophoresis (UPEP) with immunofixation; quantification of immunoglobulins at the discretion of the investigator; β2 microglobulin measurement; bone marrow plasma cell percentage; optional bone marrow cytogenetic analysis; and skeletal radiographic survey when clinically indicated. Bone marrow plasma cell percentage and image examinations (CT, MRI, or skeletal survey) performed within 4 weeks prior to first dose were acceptable.

At the baseline visit on day 1 of cycle 1, the following assessments and procedures were performed prior to the first administration of study drug: inclusion/exclusion criteria and concomitant medication review; serum or urine pregnancy test, if applicable; physical examination including skin examination and limited neurologic (motor, reflexes, and sensory) examination; vital signs, body weight, and temperature measurements; ECOG performance status; and serum chemistry, hematology, coagulation, and urinalysis testing. In addition, on day 1 of cycle 1, patients in part 1 and in stage 1 of part 2 had 12-lead ECGs performed in triplicate prior to and immediately after study drug administration (end of infusion) and 2 hours after the end of infusion. Results from tests during screening for SPEP and immunofixation, 24-hour UPEP and immunofixation, quantification of immunoglobulins at the discretion of the investigator; β2 microglobulin, bone marrow plasma cell percentage; CT, MRI, and skeletal radiographic survey were used as baseline data.

In part 1 of the study, CEP-18770 was administered as a slow intravenous bolus (approximately 1 mL per minute) on days 1, 8, and 15 of each 28-day cycle. Patients could receive up to 8 cycles of treatment. Patients who experienced clinical benefit could receive additional cycles of therapy, at the discretion of the investigator, following approval by the sponsor. Three patients were treated at each dose level, and could be enrolled simultaneously. The starting dose for patients in cohort 1 was 1.5 mg/m^2. Escalation to the next higher dose, or expansion of the existing cohort from 3 to 6 patients followed a schema.
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In part 2 of the study, CEP-18770 was administered as a slow intravenous bolus (approximately 1 mL per minute) at the MTD (2.1 mg/m^2) on days 1, 8, and 15 of each 28-day cycle in the treatment period. Patients could receive up to 8 cycles of treatment in the 32-week treatment period. Patients who experienced clinical benefit could receive additional cycles of therapy, at the discretion of the investigator, following approval by the sponsor.

If a patient had an event meeting the definition of a DLT, treatment was withheld until recovery or the occurrence of residual grade 1 for nonhematologic toxicities or residual grade 2 for hematologic toxicities, and resumed at the next lower dose. If the event was not resolved within 3 weeks, the patient was withdrawn from the study. No more than 2 dose reductions per patient were permitted.

Response to treatment was evaluated every 4 weeks during the treatment period at a clinic visit between days 21 and 27 of each cycle. In addition, patients were scheduled for a visit whenever disease progression was suspected. At the visit that occurred between days 21 and 27 of a cycle, the following assessments and procedures were performed: SPEP and immunofixation, 24-hour UPEP and immunofixation; quantification of immunoglobulins at the discretion of the investigator; bone marrow plasma cell percentage as needed to confirm CR; CT scan or MRI for patients with soft tissue plasmacytomas as needed to confirm CR; serum free light chain (FLC) assessments as needed to confirm sCR; bone marrow immunoanalysis to confirm sCR; skeletal radiographic surveys when clinically indicated; vital signs and body weight measurements; adverse event and concomitant medication inquiries; ECOG performance status; serum chemistry, hematology, coagulation, and urinalysis testing; and physical examination including skin examination and limited neurologic (motor, reflexes, and sensory) examination. On day 8 of cycle 1, clinical laboratory testing (serum chemistry, hematology, coagulation profile, and urinalysis) was done before the dose of CEP-18770. Vital signs measurements, adverse event inquiries, and concomitant medication reviews were also performed on days 1, 8, and 15 of each cycle.

An end-of-treatment visit was conducted for every patient 30 to 44 days after their last dose of study drug. The following assessments were performed at the end-of-treatment visit: when clinically indicated, CT scan or MRI, skeletal radiographic survey, and bone marrow plasma cell percentage; vital signs and body weight measurements; adverse event and concomitant medication inquiries; ECOG performance status; serum chemistry, hematology, coagulation, and urinalysis testing; and physical examination including skin examination and limited neurologic (motor, reflexes, and sensory) examination. Blood samples for pharmacokinetic and pharmacodynamic analysis were collected at specified time points during cycle 1 of part 1 and part 2.

Patients in part 2 (and patients in part 1 treated at the MTD [2.1 mg/m^2]) who completed, or discontinued study drug treatment, and who had not progressed had study visits every 8 weeks during the follow-up period until disease progression, death, or until they had been monitored for approximately 1 year after their first administration of study drug, whichever occurs first.
The following procedures/assessments were performed at each follow-up visit: response assessment, vital signs measurements; ECOG performance status; serum chemistry, hematology, and coagulation testing; physical examination including body weight, skin examination, and limited neurologic (motor, reflexes, and sensory) examination; subsequent cancer therapy inquiry; and survival.

Patients participated in the study for up to eight 28-day treatment cycles. Patients treated at the MTD (2.1 mg/m^2) also participated in a follow-up period of up to 1 year. Patient participation was expected to last approximately 9 months for patients not treated at the MTD and approximately 13 months for patients treated at the MTD of CEP-18770 (2.1 mg/m^2).

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

CEP-18770 was provided as a sterile lyophilized powder. Prior to administration, the powder was reconstituted by adding 4 mL of reconstitution solution (preservative-free, sterile solutions for injection of water, 5% mannitol, 0.9% saline, or 5% dextrose) to obtain a clear 1-mg/mL solution of CEP-18770. The infusion line was flushed with 10 to 20 mL of preservative-free, sterile solution of 5% mannitol, 0.9% saline, or 5% dextrose before and after administration of CEP-18770. The starting dose for the study was 1.5 mg/m^2. Dose escalation from the starting dose followed a modified Fibonacci sequence. Doses ranged from 1.5 to 2.4 mg/m^2. CEP-18770 was administered as a slow intravenous bolus (approximately 1 mL per minute) on days 1, 8, and 15 of each 28-day cycle. Patients could receive up to 8 cycles of treatment. Patients who experienced clinical benefit could receive additional cycles of therapy, at the discretion of the investigator, following approval by the sponsor. CEP-18770 was supplied as a sterile lyophilized powder (batches 08T004A503, 09T003A503, 09T004A503, 10T001A503, and 10T004A503).

Number of Subjects: In part 1 of this study, approximately 12 to 24 patients were to be treated with CEP-18770 to determine the MTD. In part 2 of this study, the study design was based on Simon's optimal 2-stage design (Simon 1989); 23 patients were to be treated at the MTD (2.1 mg/m^2) in the first stage of part 2. Patients treated at the MTD (2.1 mg/m^2) of CEP-18770 in part 1 were included in the first stage of part 2. If 4 or more of the 23 patients were responders (sCR, CR, VGPR, or PR) to treatment with CEP-18770, then an additional 32 patients were to be treated in stage 2 for a total of 55 patients treated in part 2.

In part 1, data from 17 patients (safety analysis set for part 1) were analyzed for safety and tabulated for efficacy. In part 2, data from 47 patients (safety analysis set part 2) were analyzed for safety and efficacy.

Efficacy Measures:

Primary: Efficacy analyses were performed on the safety analysis set for part 2 and included patients in part 1 who were treated at the MTD (2.1 mg/m^2). Efficacy data collected in part 1 was only tabulated as appropriate.

The primary efficacy variable for part 2 of this study was the ORR for patients treated with CEP-18770 at the MTD (2.1 mg/m^2). If a patient's best response was sCR, CR, VGPR, or PR, then the patient was considered as a responder. The response rate was calculated as the number of responders in the safety analysis set in part 2 divided by the number of patients in the safety analysis set for part 2. A 2-sided 95% confidence interval (CI) for the ORR was computed based on the exact binomial distribution.

Secondary: Secondary efficacy variables were defined for part 2 as follows:

- DOR was defined for responders to study drug treatment as the time interval from the date of first response to the date of disease progression. Data for patients who had not developed disease progression at the end of the study or at early withdrawal were censored at the last response assessment date. Data for patients who started other antitumor therapy without disease progression were censored at the last response assessment date before starting any of these therapies. Data for patients who died without disease progression were censored at the last tumor response date.
- TTR was defined for responders to CEP-18770 as the time interval from the date of first dose to the date of first response.
- TTP was defined for all patients treated with CEP-18770 as the time interval from the date of first dose to the date of disease progression. Data for patients who had not developed disease progression at the end of the study or at early withdrawal were censored at the last response assessment date. Data for patients who started other antitumor therapy without disease progression were censored at the last response assessment date before starting any of these therapies. Data for patients who died without disease progression were censored at the last tumor response date.

For time-to-event variables subject to right-censoring (DOR and TTP), medians were estimated using the Kaplan-Meier method and their 2-sided 95% CIs were calculated using the nonparametric method of Brookmeyer and Crowley (1982). For TTR, descriptive statistics are presented. Mean and its 95% CI were estimated using normal distribution if appropriate.

CRITERIA FOR INCLUSION:

(a) The patient had relapsed multiple myeloma that had progressed following therapies that included bortezomib and an IMiD (thalidomide or lenalidomide) either alone or in any combination.

(b) The patient had multiple myeloma, which was refractory (ie, disease progression during or within 90 days of completing treatment) to the most recent therapy, bortezomib or IMiD or any other chemotherapy,
OR
the patient did not tolerate and discontinued the most recent therapy for multiple myeloma but had recovered from its toxic effects.

(c) The patient had measurable disease defined as 1 of the following:

- serum M-protein ≥0.5 g/dL
- urine M-protein ≥200 mg/24 hours

(d) Written informed consent was obtained.

(e) The patient was a man or woman at least 18 years of age.

(f) The patient had a life expectancy of more than 3 months.

(g) The patient had an ECOG performance status of 0, 1, or 2.

(h) The patient had adequate hepatic organ function (<2.0 times the upper limit of normal [ULN] for total bilirubin, and <2.5 times ULN for aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).

(i) The patient had an absolute neutrophil count (ANC) greater than 1 x 10^9/L, hemoglobin greater than 8.0 g/dL, and platelet count greater than 50 x 10^9/L.

(j) The patient had been independent of granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) support for more than 1 week. (The patient may have received red blood cell [RBC] transfusion or supportive care such as erythropoietin and darbepoetin prior to the study in accordance with institutional guidelines.)

(k) The patient had been independent of platelet transfusion for more than 1 week.

(l) The patient may have received an allogeneic and/or autologous transplant.

(m) The patient had a creatinine clearance of 30 mL/minute or more as measured or calculated based on the Cockcroft-Gault method.

(n) Women of childbearing potential (not surgically sterile or 1 year postmenopausal) used a medically accepted method of contraception and agreed to continue use of this method for the duration of the study and for 3 months after participation in the study. Acceptable methods of contraception included abstinence, barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method.

(o) The patient, if a man, was surgically sterile, or if sexually active with a woman of childbearing potential, was currently using an effective barrier method of contraception, and agreed to continue use of this method for the duration of the study and for 3 months after the last administration of study drug.

(p) The patient was willing and able to receive outpatient treatment and laboratory monitoring at the study center where study drug was administered.

CRITERIA FOR EXCLUSION:

(a) The patient had nonmeasurable multiple myeloma, defined as less than 0.5 g/dL M-protein in serum and less than 200 mg/24 hours M-protein in urine.

(b) The patient received glucocorticoid therapy (prednisone >10 mg/day orally or equivalent) within the last 2 weeks prior to the first dose of study drug.

(c) The patient had POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy or monoclonal proliferative disorder, and skin changes [increased skin pigment, increased body hair, thickening of the skin, whitening of the nails, etc]).

(d) The patient had plasma cell leukemia.

(e) The patient received chemotherapy with approved anticancer therapeutics within 2 weeks or within 5 drug half-lives ($t_{1/2}$) or investigative anticancer therapeutics within 4 weeks or within 5 drug half-lives ($t_{1/2}$) before the first dose of study drug, whichever time was greater.

(f) The patient received radiation therapy or immunotherapy in the 4 weeks or localized radiation therapy within 1 week prior to the first dose of study drug.

(g) The patient received prior treatment with CEP-18770.

(h) The patient had used a medication known to be a potent inducer of CYP2E1, CYP2D6, or CYP3A4/5 within 4 weeks prior to the first dose of study drug.

(i) The patient had used a medication known to be a potent inhibitor of CYP2E1, CYP2D6, or CYP3A4/5 within 2 weeks prior to the first dose of study drug.

(j) The patient had major surgery within 3 weeks before the first dose of study drug.

(k) The patient had congestive heart failure (New York Heart Association Class III to IV) or had symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within the last 6 months.

(l) The patient had an acute infection requiring systemic antibiotics, antiviral agents, or antifungal agents within 2 weeks before the first dose of study drug.

(m) The patient had a known or suspected human immunodeficiency virus (HIV) infection on the basis of medical history.

(n) The patient had a nonhematologic malignancy within the past 3 years except for the following: adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or breast, or prostate cancer (Gleason grade <6 with prostate specific antigen levels within the normal range).

(o) The patient had myelodysplastic or myeloproliferative syndrome.

(p) The patient had significant neuropathy (grade 3 or 4 or grade 2 with pain).

(q) The patient was a pregnant or lactating woman. (Any women becoming pregnant during the study were withdrawn from the study.)

(r) The patient had known central nervous system (CNS) involvement.

(s) The patient had any serious psychiatric or medical condition that could interfere with treatment or study procedures, place the patient at unacceptable risk, or confound the ability of investigators to interpret study data.

(t) The patient had known hypersensitivity to mannitol or hydroxypropyl betadex.

Safety Measures: Safety and tolerability were assessed by evaluating the following: occurrence of adverse events throughout the study; clinical laboratory (serum chemistry, hematology, urinalysis, and coagulation profile) test results at specified time points throughout the study; ECGs in triplicate at specified time points prior to and after study drug administration; vital signs (blood pressure and pulse) measurements and physical examination findings, including body weight measurements, at specified time points throughout the study; ECOG performance status at specified time points throughout the study; concomitant medication usage throughout the study.

Pharmacokinetic Parameters: The following pharmacokinetic parameters were calculated, as appropriate, from blood samples collected at specified time points following study drug administration on days 1 and 15 of cycle 1 during parts 1 and 2 of the study:

- maximum observed drug concentration (C_{max})
- time to maximum observed drug concentration (t_{max})
- area under the plasma concentration-time curve from time 0 to 6 hours post-dose (AUC_{0-6})
- area under the plasma concentration-time curve from time 0 to the last measurable time point (AUC_{0-t})
- area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$)

Pharmacodynamic Parameters: Blood samples, and, where available, bone marrow samples, were to be analyzed for pharmacodynamic biomarker or response. These may have included assays of proteasome inhibition, in which case, the maximum proteasome inhibition and an area under the curve estimate of proteasome inhibition over time were also determined. Additional analyses may have included analyses of the effects of CEP-18770 on signaling pathways in both normal and malignant blood- or marrow-derived cells.

Study Population: All study population summaries (except for patient disposition) were summarized by study phase. Part 1 data were summarized by assigned dose cohort and overall using the safety analysis set for part 1. Part 2 data were summarized using the safety analysis set for part 2.

DISPOSITION OF SUBJECTS: Of the 61 patients enrolled in this study, 17 (28%) patients in part 1 and 47 (77%) patients in part 2 received at least 1 dose of study drug and were evaluated for safety. Fifteen (25%) patients were in the MTD determination set. Eight patients had protocol violations during the study; 1 patient had a protocol violation in part 1 of the study and study participation was terminated and 7 patients in part 2 had violations and continued in the study. Fifteen (25%) patients completed cycle 1 treatment for part 1 and, according to the protocol, were considered to have completed the study. Two (3%) patients discontinued treatment for part 1, both due to adverse events.

All 44 patients who enrolled in part 2 of the study discontinued the study. The most frequent reason for withdrawal was disease progression, which occurred for 31 (70%) patients. One patient (2%) died during the study, 2 (5%) patients withdrew due to adverse events, 6 (14%) patients withdrew consent, and 4 (9%) patients withdrew due to other reasons. The other reasons for withdrawal were treatment delayed more than 2 weeks for ECOG performance score=3, lack of response, no clear evidence of clinical benefit, medical decision due to stable disease, and herpes zoster.

In part 1 of the study, the mean (standard deviation) age of all patients enrolled in the study was 64.5 (11.03) years; the median (range) age was 68.0 (44.0 to 82.0) years. The majority (71%) of patients were white; 65% of the patients were men and 35% were women.

At baseline, 47% of patients had an ECOG status of 0, 49% had a score of 1, and 4% had a score of 2. The following neurologic conditions were observed at baseline: 14 (30%) patients had grade 1 paresthesia, 7 (15%) patients had grade 2 paresthesia, 2 (4%) patients had grade 1 peripheral motor neuropathy, 1 (2%) patient had grade 2 peripheral motor neuropathy, 18 (38%) patients had grade 1 peripheral sensory neuropathy, 6 (13%) patients had grade 2 peripheral sensory neuropathy, and 5 (11%) patients had grade 1 neuralgia.

Summaries of medical history, prior and concomitant medications, ECG findings, and abnormal physical examination findings for patients in parts 1 and 2 of the study are provided. A total of 8 patients had protocol violations during parts 1 and 2 of the study. One patient in part 1 (1.5-mg/m^2 group) did not meet inclusion criteria and participation in the study was terminated. Of the 7 patients in part 2 of the study who had protocol violations, the following types of violations occurred: exclusion criteria (3 patients), good clinical practice (GCP) guidelines (1 patient), study medication (2 patients), and other (3 patients). In part 2, 3 patients were approved to continue and for the other 4 patients the violation was acknowledged, no action was taken, and the subjects completed participation.

EFFICACY EVALUATION: None of the patients had a response categorized as sCR, CR, or VGPR. A PR was observed for 4 (9%) patients and 26 (55%) patients had stable disease. The ORR was 9% (95% CI: 2.37, 20.38). The median time to first response for the 4 patients who responded to study treatment was 1.4 months, with a range of 0.8 to 8.1 months.

Of the 4 patients with responses, 1 patient subsequently had progressive disease 2.8 months after achieving response. Three patients did not develop disease progression or die before discontinuing the study and their data were censored. Therefore, the median duration of response for those patients who responded to study treatment could not be determined due to the censoring of data. According to the Kaplan-Meier estimates, 1 patient maintained a response for 3 months).

The median TTP, estimated by the Kaplan-Meier method, was 2.5 months, with a lower 95% CI boundary of 1.6 and an upper 95% CI boundary of 2.8. According to the Kaplan-Meier estimates, 50% patients were progression free at 2 months and 4% of patients were progression free at 10 months.

SAFETY EVALUATIONS: It should be noted that data for patients who were administered CEP-18770 at the MTD of 2.1 mg/m^2 in part 1 of the study are also included in safety results for patients in part 2 of the study.

In part 1 of this study, the mean numbers of treatment cycles received by patients in the safety analysis set were similar for all treatment groups, except for the 1.8-mg/m^2 group, which was 7.3 cycles. In the other groups, the following number of treatment cycles were observed: 3.3 treatment cycles in 1.5-mg/m^2 group, 3.0 treatment cycles in the 2.1-mg/m^2 group, and 3.4 treatment cycles in the 2.4-mg/m^2 group. The mean RDIs were 78.5%, 91.9%, 83.9%, and 72.9% in the 1.5-mg/m^2 group, 1.8-mg/m^2 group, 2.1-mg/m^2 group, and 2.4-mg/m^2 group, respectively.

In part 2 of this study, the mean number of treatment cycles received by patients was 2.8 cycles. The mean RDI was 83.0%.

In part 1 of this study, every patient who received study drug treatment had at least 1 adverse event. Six patients had at least 1 serious adverse event during part 1 of the study, 1 (25%) in the 1.5-mg/m^2 group, 2 (67%) in the 1.8-mg/m^2 group, and 3 (43%) in the 2.4-mg/m^2 group.

All of the following serious adverse events were reported in 1 patient each: nausea, vomiting, herpes zoster, urinary tract infection, and spinal cord compression in the 2.4-mg/m^2 group; spinal compresssion fracture and renal failure acute in the 1.5-mg/m^2 group, and femur fracture and renal failure in the 1.8-mg/m^2 group. Herpes zoster, spinal cord compression, and nausea and vomiting were considered related to study drug treatment by the investigator; the other serious adverse events were considered not related to study drug treatment.

Two patients in the 1.5-mg/m^2 group and 4 patients in the 2.4-mg/m^2 group withdrew from part 1 of the study due to nonserious adverse events. In the 1.5-mg/m^2 group, 1 patient had blood creatinine increased (nonserious and not related to study drug treatment) and 1 patient had swelling face (nonserious and related to study drug treatment). In the 2.4-mg/m^2 group,1 patient had urinary tract infection (serious and not related to study drug treatment), 1 patient had spinal cord compression (serious and related to study drug treatment), 1 patient had rash generalized (nonserious and related to study drug treatment), and rash maculo-papular (nonserious and related to study drug treatment).

In part 2 of this study, 45 (96%) patients who received study drug treatment had at least 1 adverse event. Eighteen (38%) patients had at least 1 serious adverse event during part 2 of the study. The following events were observed in more than 1 patient: pyrexia (4 patients), pneumonia (3 patients), back pain (2 patients), and renal failure (2 patients). Most of the serious adverse events that occurred during part 2 of the study were considered not related to study drug treatment by the investigator, with the exception of events in 5 patients. The following 5 patients had serious adverse events that were considered related to study drug treatment: patient PPD had palmar-plantar erythrodysaesthesia syndrome, patient PPD had pneumonia, patient PPD had 2 events of pyrexia, patient PPD had renal failure, and patient PPD had a staphylococcal infection.

Five patients withdrew from part 2 of the study due to adverse events. The events were neutropenia, palmar-plantar erythrodysaesthesia syndrome, and thrombocytopenia (patient

PPD rash maculo-papular (patient PPD spinal disorder (patient PPD back pain (patient PPD and thrombocytopenia (patient PPD All of these events were nonserious except for the palmar-plantar erythrodysaesthesia syndrome and back pain. The majority (71%) of these events were considered related to study drug treatment by the investigator. Spinal disorder and back pain were considered not related to study drug treatment.

Most adverse events were grade 1 or 2 in severity during part 1 of the study. Of the 17 patients in the safety analysis set, grade 3 and grade 4 adverse events were as follows: grade 3 adverse events reported for more than 1 patient in a cohort were leukopenia (2 patients in 2.4-mg/m^2 group), thrombocytopenia (3 patients in 2.4-mg/m^2 group), and herpes zoster (2 patients in 2.4-mg/m^2 group). Grade 4 adverse events, each of which occurred once, were spinal compression fracture in 1.5-mg/m^2 group; and urinary tract infection, thrombocytopenia, and hypotension in 2.4-mg/m^2 group. Grade 3 adverse events considered related to treatment with study drug for more than 1 patient were thrombocytopenia 2 (29%) patients and herpes zoster 2 (29%) patients in the 2.4-mg/m^2 group. There was 1 grade 4 treatment-related adverse event of thrombocytopenia, which occurred in the 2.4-mg/m^2 group.

Most adverse events were grade 1 or 2 in severity during part 2 of the study. Of the 47 patients treated at the MTD, grade 3, grade 4, and grade 5 adverse events were as follows: grade 3 adverse events reported for at least 5% of patients were anemia and thrombocytopenia each in 9 (19%) patients, neutropenia in 7 (15%) patients, and leukopenia, pneumonia, platelet count decreased, and white blood cell count decreased each in 3 (6%) patients. Grade 4 adverse events were thrombocytopenia in 12 (26%) patients, neutropenia in 3 (6%) patients, and sepsis, platelet count and hyperuricemia each in 1 (2%) patients. There were 2 grade 5 events: general physical health deterioration 1 (2%) patient and renal failure acute 1 (2%) patient. Grade 3 adverse events considered related to treatment with study drug for more than 1 patient were thrombocytopenia in 9 (19%) patients, neutropenia in 7 (15%) patients, platelet count decreased in 2 (4%) patients, and white blood cell count decreased in 2 (4%) patients. Grade 4 treatment-related adverse events were thrombocytopenia in 11 (23%) patients, and neutropenia and platelet count decreased each in 1 (2%) patient.

Deaths: In part 1 of the study, no patient had a fatal adverse event within 30 days after the last dose of study drug. Three patients died more than 30 days after the last dose of study drug, 1 patient in the 1.5-mg/m^2 group, 1 patient in the 1.8-mg/m^2 group, and 1 patient in the 2.4-mg/m^2 group died. All of these deaths were due to disease progression.

In part 2 of the study, one patient died within 30 days after the last dose of study drug and 3 patients died more than 30 days after the last dose of study drug. All of these deaths were due to disease progression or complications resulting from disease progression.

OTHER SAFETY EVALUATIONS: During parts 1 and 2 of the study, there was no evidence of any clinically meaningful trends in mean changes from baseline for any clinical laboratory variable. Overall worst NCI CTCAE (version 4.0) grades for selected serum chemistry tests were summarized.

During part 1 of the study, there was 1 grade 4 abnormal serum chemistry test result (high uric acid) and 7 grade 3 abnormal serum chemistry test results. The most frequently occurring grade 3 laboratory result was decreased sodium, reported in 1 patient in each of the 4 dose groups. Patient PPD in the 1.5-mg/m^2 group, had a grade 3 adverse event of hyponatremia, which was reported as a nonserious adverse event on day 17. No action was taken with regard to study medication and the event resolved with no residual effects by day 22.

During part 2 of the study, there were 6 grade 4 abnormal serum chemistry test results (4 increased calcium and 2 increased uric acid) and 15 grade 3 abnormal serum chemistry test results. The most frequently occurring grade 3 chemistry test result was low sodium occurring in 6 patients. Low phosphorus occurred in 3 patients; high creatinine in 2 patients; and high calcium, high glucose, high GGT, and low potassium in 1 patient each. Three patients had grade 3 laboratory test results reported as adverse events; no action was taken with regard to study drug for any of these events and all 3 events were considered not related to study drug treatment. Patient PPD had a nonserious event of grade 3 creatinine increased on day 45 that decreased to grade 2, then grade 1 and continued. Patient PPD had a serious event of grade 3 hyponatremia on day 31 that decreased to grade 1 and continued. Patient PPD had a nonserious event of grade 3 hypokalemia on day 71 that resolved with no residual effect on day 78.

Overall worst grades for selected serum hematology tests results were also summarized. The most frequently occurring serum hematology abnormality was decreased hemoglobin (61 patients total during parts 1 and 2 of the study). However, most of these abnormalities were grade 1 and 2. One patient had a grade 4 decreased hemoglobin and 7 patients had a grade 3 decreased hemoglobin. The most frequent grade 3 and 4 hematology abnormality was decreased platelets (30 patients total). Thirteen patients had grade 4 decreased platelets and 17 patients had grade 3 decreased platelets. Grade 4 serum hematology abnormalities were also observed for decreased absolute lymphocytes (4 patients), and decreased absolute neutrophils (4 patients). Grade 3 abnormalities were also observed for WBC (16 patients), absolute lymphocytes (11 patients), and absolute neutrophils (10 patients).

Three patients in part 1 of the study, and 9 patients in part 2 had at least 1 potentially clinically significant vital sign abnormality. The most frequently occurring vital sign abnormality was a weight decrease of at least 10% occurring in 5 patients.

Few patients with physical examinations at baseline and postbaseline had shifts from normal to abnormal findings in parts 1 and 2 of the study. In both parts of the study, the most frequent shift from normal to abnormal was seen in physical examinations of the skin.

One patient in part 1 of the study (2.4-mg/m^2 group) and 2 patients in part 2 of the study had a shift in ECG findings from normal at baseline to abnormal.

In part 1 of the study, the following numbers of patients had ECOG endpoint values that deteriorated after baseline: 2 patients (1.5-mg/m^2 group) and 5 patients (2.4-mg/m^2 group). In part 2 of the study, 12 (26%) patients had an ECOG endpoint value that deteriorated from baseline. In part 1, a small number of patients had worsening of the following: paresthesia (1 patient each in the 1.5-mg/m^2 group, 1.8-mg/m^2 group, and 2.4-mg/m^2 group), peripheral motor neuropathy (1 patient in the 1.8-mg/m^2 group, and 2 patients in the 2.1-mg/m^2 group), peripheral sensory neuropathy (1 patient in the 1.8-mg/m^2 group), and neuralgia (neuropathic pain, 1 patient in the 1.8-mg/m^2 group and 1 patient in the 2.4-mg/m^2 group). In part 2 of the study, a relatively small number of patients had a worsening of the following: paresthesia (2 patients), peripheral motor neuropathy (2 patients), peripheral sensory neuropathy (2 patients), and neuralgia (neuropathic pain, 4 patients).

PHARMACOKINETIC EVALUATION: The CEP-18770 plasma concentrations and pharmacokinetic parameters in individual patients are presented in a separate pharmacokinetics report (report DP-2011-010).

Due to sample processing errors and analytical difficulties, the concentrations in most of the 4-, 8-, 24-, 48-, 96- and 144-hour samples in the 2.1-mg/m^2 dose group were not reportable. Based on the profiles from the other dose groups, the terminal phase was best described by samples obtained after 24 hours. Therefore, the half-lives reported for the 2.1-mg/m^2 dosage group likely underestimate the true values.

CEP-18770 was detected in the trough samples obtained predose on days 8 and 15 in the 1.5-, 1.8-, and 2.4-mg/m^2 dose groups. Furthermore, although variable, the AUC values from the 1.5-, 1.8-, and 2.4-mg/m^2 dose groups suggest that CEP-18770 accumulated when administered once weekly. A qualitative assessment of the AUC values also suggests that CEP-18770 exposure increased with dose over the range tested.

PHARMACODYNAMIC EVALUATION: Due to the decision to stop the study, there was no pharmacodynamic analysis.

CONCLUSION: During part 1 of the study, 2.1 mg/m^2 was determined to be the MTD after 2 DLTs (1 patient with grade 3 rash [verbatim: maculo-papular rash] and 1 patient with grade 3 thrombocytopenia) were observed at the maximum administered dose of 2.4 mg/m^2. None of the patients in part 2 of the study had a response categorized as sCR, CR, or VGPR. A PR was observed for 4 (9%) patients; and 26 (55%) patients had stable disease. The ORR was 9% (95% CI: 2.37, 20.38). The median time to first response for the 4 patients who responded to study treatment was 1.4 months, with a range of 0.8 to 8.1 months. Of the 4 patients with a PR, 1 patient subsequently had disease progression; therefore, the median duration of response for those patients who responded to study treatment could not be determined due to the censoring of data. According to the Kaplan-Meier estimates, 50% of patients maintained treatment benefit for 3 months. The median TTP, estimated by the Kaplan-Meier method was 2.5 months, with a lower 95% CI boundary of 1.6 and an upper 95% CI boundary of 2.8. According to the Kaplan-Meier estimates, 50% patients were progression free at 2 months and 4% patients were progression free at 10 months. Since the magnitude of the effect did not reach a clinically meaningful response rate (sCR, CR, or VGPR) prespecified in the study protocol, no further development of CEP-18770 is planned for this indication. The pharmacokinetic data obtained in this study suggest that CEP-18770 exposure increased with dose over the range tested and accumulated with once-weekly intravenous administration. The myelosuppressive effects of the regimen were as expected and severe nonhematologic adverse events were relatively infrequent.

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