Synopsis

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Study title:
A Continuous Administration or Readministration Study JNJ-26866138 (bortezomib) in Patients with Relapsed or Refractory Multiple Myeloma

Investigators:
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Investigator Sites:
Tokai University Hospital, National Cancer Center Hospital, National Cancer Center Hospital East, Aichi Cancer Center

Published papers (cited references):
None (For cited references, see Chapter 15.)

Study Period:	**Developmental Phase:**
Registered date of first subject: December 16, 2004 Completed date of last subject: November 13, 2006	Phase II

Objectives:
Continuous administration group:
To assess the safety and efficacy of JNJ-26866138 in long-term administration to subjects who completed the phase I/II study.
Readministration group:
To assess the safety and efficacy of JNJ-26866138 in readministration at the recommended dose (RD) in Japan to subjects who participated in the phase I/II study or the continuous administration group.

Study Methods:
This study was a non-randomized open-label study in patients with relapsed or refractory multiple myeloma, where JNJ-26866138 (bortezomib) was administered to the following two patient groups: i) "a continuous administration group" of patients to continuously receive JNJ-26866138 treatment following the completion of treatment repeated up to 6 cycles in the clinical phase I/II study (hereinafter referred to as phase I/II study), and ii) "a readministration group" of patients possible to receive readministration at a recommended dose of JNJ-26866138 in Japan as an initial dose after the domestic RD is determined.
Continuous administration group
Enrolled patients as subjects were those who showed an antitumor effect of ≥ NC in findings up to cycle 6 in the phase I/II study and were considered to obtain specific benefits from continuous administration of the investigational drug by the investigator or subinvestigator.
JNJ-26866138 was administered to the patients at intravenous bolus doses being used at the end of the phase I/II study, twice weekly for 2 weeks (Days 1, 4, 8 and 11) followed by a 10-day rest period (Days 12-21). This was considered one cycle (3-week cycle), and the study design required at least 2 cycles (a total of 8 cycles from the phase I/II study).
After that, referring to study designs of the phase III studies, continuous administration studies and readministration studies in Europe and the United States, and considering the subjects' burden and safety, etc., JNJ-26866138 was added as intravenous bolus doses once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23-35). This was considered one cycle (5-week cycle). The 3-week cycle or 5-week cycle could be appropriately selected at each cycle according to the patient's clinical condition and personal reason, etc.
Readministration group
After the domestic RD of the investigational drug was determined in the phase I/II study, the enrolled patients as subjects were those who were expected to obtain specific benefits from readministration at the domestic RD and had no problem with safety in the phase I/II study or in the continuous administration group in the present study.
JNJ-26866138 was administered to the patients using the domestic RD as an initial dose in the 3-week cycle for 8 cycles from the start of readministration. After that, considering the subjects' burden and safety, etc. as in the above continuous administration group, the study was designed to allow an appropriate selection from the 3-week cycle or 5-week cycle at each cycle.
For subjects registered in the continuous administration group at low doses not reaching the domestic RD, if they had completed at least 2 cycles as continuous administration (a total of 8 cycles from the phase I/II study) and were eligible for the readministration group after the domestic RD was determined, they could terminate the study in the continuous administration group to be registered in the readministration group.

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Sample Size (at planning and at analysis):

At planning: 33 (The number was increased or reduced depending on the status of patient accrual in the phase I/II study. The registration of new patients for this study was cut off at the time of approval for JNJ-26866138.)

At analysis: Number of enrolled patients: 13 (8 in continuous administration group, 5 in readministration group)
Primary efficacy analysis set: 13 patients
Safety analysis set: 13 patients

Diagnosis and Major Inclusion Criteria:

Continuous administration group

Patients who met all of the following criteria were eligible as subjects for the study.

1) Patients who completed the administration/observation up to cycle 6 in the phase I/II study.
2) Patients those who showed an antitumor effect of ≥ NC in findings up to cycle 6 in the phase I/II study and were considered to obtain specific benefits such as antitumor effects, pain relief, and an improvement in PS, etc. from continuous administration of JNJ-26866138 by the investigator or subinvestigator.
3) Patients who had the following organ functions within 7 days before the start of this study (N means an upper limit of institutional standard range).
   Examination data in the phse I/II study could be used for registration in this study.
   1. Bone marrow function Neutrophil count[*1] ≥1,000/mm^3
      Platelet count[*2] ≥ 50,000/mm^3
      Hemoglobin[*2] ≥ 8.0 g/dL
   [*1] Value without G-CSF treatment within 7 days before the examination.
   [*2] Value without blood transfusion within 7 days before the examination.
   2. Hepatic function Serum bilirubin total ≤ 1.5 × N
      ALT (SGPT) ≤ 2.5 × N
      AST (SGOT) ≤ 2.5 × N
   3. Renal function Creatinine clearance ≥ 30 mL/min
   4. Electrolytes Serum calcium corrected ≤ 12.5 mg/dL (3.1 mmol/L)
4) Female patients who are either postmenopausal (≥ 1 year after the last menstruation) or surgically sterilized, or willing to use an acceptable method of birth control (e.g., a hormonal contraceptive, contraception device) during the study. Male patients who agree to use an acceptable method for contraception for the duration of the study.
5) Patients who are informed of the details of the study with the prescribed informed consent form and other written information for subjects by the investigator or subinvestigator (and clinical trial collaborator) and have voluntarily given written informed consent for study participation.

Readministration group

Patients who met all of the following criteria were eligible as subjects for the study.

1) Patients who did not show adverse drug reactions of ≥ Grade 3 non-hematological toxicities or Grade 4 hematological toxicities in the phase I/II study or in the continuous administration group in this study.
2) Patients who were considered to obtain specific benefits such as antitumor effects, pain relief, and an improvement in PS, etc. from readministration of JNJ-26866138 at the domestic RD by the investigator or subinvestigator.
3) Patients who had the following organ functions within 14 days before the start of this study (N means an upper limit of institutional standard range).
   Examination data in the phase I/II study or in the continuous administrating group in this study could be used for registration in this study.
   1. Bone marrow function Neutrophil count[*1] ≥1,000/mm^3
      Platelet count[*2] ≥ 50,000/mm^3
      Hemoglobin[*2] ≥ 8.0 g/dL
   [*1] Value without G-CSF treatment within 7 days before the examination.
   [*2] Value without blood transfusion within 7 days before the examination.
   2. Hepatic function Serum bilirubin total ≤ 1.5 × N
      ALT (SGPT) ≤ 2.5 × N
      AST (SGOT) ≤ 2.5 × N
   3. Renal function Creatinine clearance ≥ 30 mL/min
   4. Electrolytes Serum calcium corrected ≤ 12.5 mg/dL (3.1 mmol/L)
4) Patients with Karnofsky Performance Status (PS): ≥ 60

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5) Patients with no evident effect of prior treatment who met the following criteria by the initial day of treatment with the investigational drug in the relevant drug group.

1. Chemotherapy, thalidomide, and interferon:
   No treatment period of ≥ 3 weeks following prior therapy (≥ 6 weeks following nitrosoureas)
2. Prednisolone ≥ 10 mg/day or equivalent steroid therapy:
   No treatment period of ≥ 3 weeks following prior therapy
3. Immunotherapy (except for interferon), antibody therapy, radiation therapy:
   No treatment period of ≥ 4 weeks following prior therapy
4. Autologous peripheral-blood stem cell transplantation:
   No treatment period of ≥ 8 weeks following prior therapy
5. Blood plasma exchange and extensive surgery*:
   No treatment period of ≥ 4 weeks following prior therapy

* Kyphoplasty is not included in the extensive surgery.

6. Treatment with the investigational drug: ≥ 10-day rest period from treatment given immediately before
7. Treatment with other investigational drugs: Patients treated with any investigational drug that has not been marketed in Japan except JNJ-26866138 must have their last dose at least 12 weeks after the completion of treatment, irrespective of the purpose of treatment.

6) Female patients who are either postmenopausal (≥ 1 year after the last menstruation) or surgically sterilized, or willing to use an acceptable method of birth control (e.g., a hormonal contraceptive, contraception device) for the duration of the study. Male patients who agree to use an acceptable method for contraception for the duration of the study.

7) Patients who are informed of the details of the study with the prescribed informed consent form and other written information for subjects by the investigator or subinvestigator (and clinical trial collaborator) and have voluntarily given written informed consent for study participation.

8) If patients are transferred to this study from the continuous administration group, those who completed the treatment/observation for 2 cycles in the continuous administration group (a total of 8 cycles from the phase I/II study).

Investigational drug, dosage and treatment methods, lot number:

Dosage

JNJ-26866138 was administered to the continuous administration group at the dose level (0.7, 1.0 or 1.3 mg/m^2) being used at the end of the cycle in the phase I/II study, and to the readministration group at the domestic RD (1.3 mg/m^2) determined in the phase I/II study.

Treatment methods

JNJ-26866138 solution was administered as intravenous bolus doses over 3 to 5 seconds, and flushed with physiological saline. Prior to treatment, at least 72-hour treatment interval was taken.

The dose was maintained during the cycle unless the criterion of dose reduction in the "Criteria for drug rest or dose reduction" was met. If the patient's body weight significantly increased or decreased (an increase or decrease of ≥ 3.6 kg is observed), body weight measurement was conducted additionally to the observation schedule to re-calculate the dose.

Lot number of JNJ-26866138

02DA, 03DG, V06PE9675

Treatment Period:

JNJ-26866138 treatment could be repeated as long as the patient did not meet the "Discontinuation Criteria" or "Termination Criteria" and met the "Conditions to start the next cycle".

Continuous administration group

JNJ-26866138 treatment was continued in the 3-week cycle at the dose level being used at the end of the phase I/II study. If the patient did not meet the "Criteria for drug rest or dose reduction", the investigational treatment schedule in each cycle could be selected appropriately from the 3-week cycle or 5-week cycle at the investigator's or subinvestigator's judgment after the completion of treatment/observation for 2 cycles in the clinical study (a total of 8 cycles from the phase I/II study).

For subjects registered in the continuous administration group at low doses not reaching the domestic RD, if they had completed at least 2 cycles as continuous administration (a total of 8 cycles from the phase I/II study) and were eligible for the readministration group after the domestic RD was determined, they could terminate the study in the continuous administration group and be registered in the readministration group.

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Readmitration group

JNJ-26866138 was administered in the 3-week cycle at the domestic RD (1.3 mg/m^2) over 8 cycles from the start of readministration. If the subject did not meet the "Criteria for drug rest or dose reduction", the investigational treatment schedule in each cycle could be selected appropriately from the 3-week cycle or 5-week cycle at the investigator's or subinvestigator's judgment in the ninth and later cycles.

Endpoints

Safety: Adverse events, anamnesis, neurological examination, physical examination, body weight, cardiopulmonary function test, laboratory examinations, performance status, prognostic factor (only for continuous administration group)

Efficacy: Evaluation of antitumor effect, serum or urinary M protein, proportion of plasma cells in bone marrow, soft tissue tumor, osteolytic lesions, serum calcium corrected

Statistical Methods:

Safety

The following tabulation and analysis were conducted in the safety analysis set.

1) Adverse events
- Treatment-emergent signs and symptoms were the events to be analyzed. The tabulation of events was conducted based on Preferred Terms (PT) in MedDRA/J.
- For individual adverse events (PT), the number of patients with each event, the incidence, and the prevalence were tabulated by cycle.
- For individual adverse events (PT) and organ classes, the number of patients with events and the incidence were tabulated. In addition, these were tabulated by severity (NCI-CTC Grade), causal relationship with the investigational drug, and seriousness.

2) Adverse drug reactions
- The tabulation and analysis were conducted similarly to adverse events.

3) Physical examination, performance status, cardiopulmonary function test, prognostic factor (continuous administration group only)
- Descriptive statistics were calculated for quantitative items by testing time, and classified tabulation was conducted for qualitative items.

4) Laboratory examinations
- For quantitative items, descriptive statistics of test data and change from baseline were calculated by testing time, and a comparison with baseline was conducted by the Wilcoxon signed rank test. For qualitative items, classified tabulation was conducted.
- The test data were classified into low values, normal values and high values according to the testing laboratory's standard range by testing time to prepare tabulation tables.
- For low values, normal values and high values, a shift table between before and after treatment was prepared. In this case, a posttreatment value was considered a nadir over posttreatment tests in this study. [That is, if there was a mixture of low values (high values) and normal values, it was considered a low value (high value). However, if there is a mixture of low values and high values, it was considered unidentifiable.]
- For patients who had Grade 1 hematological toxicities (white blood cell count decreased, neutrophils decreased, platelets decreased, hemoglobin decreased) considered adverse drug reactions whose relationship with the investigational product could not be ruled out, a lowest value (nadir) of the relevant hematological examination and the time (number of days) to first recognition of the nadir were obtained. If the outcome was recovered or relieved, the time from nadir to the outcome was calculated. The baseline was considered a test value before the start of treatment with JNJ-26866138 in this study.

5) Neurological examination
- Classified tabulation was conducted by testing time. Descriptive statistics were calculated for the score (total) obtained from scoring provided separately for each testing time.

Efficacy

Overall response was considered to be a primary endpoint. For the continuous administration group, the phase I/II study data were also included in the evaluation. The following tabulation and analysis were conducted in the full analysis set.

1) Primary endpoint
- For overall response, the point estimate and 90% and 95% confidence intervals two-tailed (the exact method) were calculated.
- For the rate of CR, the point estimate and 90% and 95% confidence intervals two-tailed were also calculated.

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- For the rate of disease response (CR+PR+MR), the point estimate and 90% and 95% confidence intervals two-tailed were also calculated.
- For the rate of ($CR+CR^{IF+}$), the point estimate and 90% and 95% confidence intervals two-tailed were also calculated.
- In patients of the continuous administration group, cross-tabulation of overall response was conducted between the phase I/II study and the present study.

2) Serum or urinary M protein concentration, proportion of plasma cells in bone marrow, soft tissue tumor
- Descriptive statistics were calculated by testing time.

3) Analysis in partial population
- Overall response in each partial population was tabulated, and the number of patients with response and the response rate were calculated.

Summary/Conclusion:

(1) Continuous administration group

Eight patients participating in the phase I/II study were enrolled in the continuous administration group. Their dose levels in the phase I/II study were dose level 2 (1.0 mg/m^2) in 2 patients and dose level 3 (1.3 mg/m^2) in 6 patients. The mean number of treatment cycles in the continuous administration group was 10.0 and the mean duration of treatment was 253.4 days. In 7 of 8 patients in the continuous administration group, treatment was possible for 9 or more cycles started from the phase I/II study. The maximum number of cycles was 26 (a total of 32 cycles from the phase I/II study), and the duration of treatment was as long as 673 days. No dose reduction was conducted in the continuous administration group. On the other hand, the percentage of postponed starting cycles to following cycles was 40.3%, and treatment was skipped 16 times in 4 of 8 patients. The percentage of postponed starting cycles was similar compared with the phase I/II study (42.5%), but treatment was more frequently skipped in the continuous administration group (phase I/II study: 4 times in 3 of 34 patients).

Regarding antitumor effect (overall response), the response rate in the continuous administration group was 75.0% (6/8), and the details of the response cases were CR in 1 patient and PR in 5 patients.

In a comparison with the phase I/II study in antitumor effect (overall response) obtained, an enhancement of antitumor effect (change from CR^{IF+} to CR) was observed in 1 patient.

Adverse events were observed in all patients of the continuous administration group, and at least 1 adverse event was considered to be related to JNJ-26866138 (adverse drug reactions) in all the patients. ≥ Grade 3 adverse events were observed in 6 patients (75.0%, 6/8) and ≥ Grade 4 adverse events and serious adverse events were observed in 1 patient (12.5%, 1/8), respectively. Among PTs, the adverse event observed most was rash and the incidence was 62.5% (5/8).

If the status of adverse events is compared with that in the phase I/II study, the incidence of adverse events leading to treatment skip or postponed starting cycle was higher in the continuous administration group. The incidence of adverse events leading to dose reduction was higher in the phase I/II study. The serious adverse event reported in 1 patient of the continuous administration group was "renal cell cancer, stage unknown", and the serious lung disorder reported in the phase I/II study was not observed. Among ≥ Grade 3 adverse events, the event not observed in the phase I/II study but observed only in the continuous administration group was hypercalcaemia, whose causal relationship with JNJ-26866138 was "Not related". On the other hand, among ≥ Grade 3 adverse events observed in ≥ 10% in the phase I/II study, the events not observed in the continuous administration group were thrombocytopenia and platelet count decreased. ≥ Grade 3 lung disorders observed in the phase I/II study including pneumonia, pleural effusion, interstitial lung disease and pneumothorax were not observed in the continuous administration group.

As a result of continuous administration to patients treated with JNJ-26866138 in the phase I/II study, long-term treatment was possible. Treatment was possible for 26 cycles at maximum (a total of 32 cycles from the phase I/II study) during the study period (to the time of approval). In efficacy, 1 patient showed an enhancement of antitumor effect (overall response) due to continuous administration. As for safety, there was no significant change in the status of adverse events compared with the phase I/II study. Unlike the phase I/II study, no serious lung disorder was reported.

(2) Readministration group

In the readministration group, a total of 5 patients were reported: 4 patients from the phase I/II study and 1 patient from the continuous administration group. The dose levels in the 4 patients from the phase I/II study were dose level 1 (0.7 mg/m^2) in 1 patient and dose level 3 (1.3 mg/m^2) in 3 patients. The mean number of treatment cycles in the readministration group was 3.0 and the mean duration of treatment was 65.2 days. The study was discontinued in 4 of 5 patients up to 3 cycles, and the maximum number of treatment cycles was 8.

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The percentage of postponed starting cycles to following cycles was 60.0%. Treatment was skipped 6 times in 1 of 5 patients.

Regarding antitumor effect (overall response), the response rate in the readministration group was 20.0% (1/5). The details of the response cases were PR in 1 patient, NC in 1 patient, PD in 2 patients, and NE in 1 patient.

Adverse events were observed in all patients of the readministration group, and at least 1 adverse event was considered to be related to the investigational drug (adverse drug reactions) in all the patients. Among adverse events by PT, the events observed most were lymphopenia, anaemia and fatigue, and the incidence was 80.0% (4/5), respectively. ≥ Grade 3 adverse events were observed in all patients (100.0%, 5/5). ≥ Grade 4 adverse events were observed in 1 patient (20.0%, 1/5). No serious adverse events were observed. Grade 3 adverse events observed most in the readministration group were lymphopenia and anaemia. All the Grade 3 adverse events observed in ≥ 2 patients were hematological toxicities. As a Grade 4 adverse event, hypercalcaemia occurred in 1 patient. The adverse event leading to discontinuation of treatment occurred in 1 patient. The adverse events leading to treatment skip or postponed starting cycle and dose reduction occurred in 2 patients, respectively.

As a result of readministration to patients treated with JNJ-26866138 in the phase I/II study or in the continuous administration group in the present study, adverse events occurred in all patients, but no serious adverse events were reported. ≥ Grade 3 adverse events occurred in all patients. The major adverse events were hematological toxicities. The results were not so different from the phase I/II study results.

(3) Overall conclusions

This study was conducted in patients treated with JNJ-26866138 in the phase I/II study to assess the safety and efficacy in continuous administration or readministration of the drug.

In efficacy, a patient showed an enhancement of antitumor effect (overall response) due to continuous administration. Some patients showed response to readministration. As for safety, regarding the status of adverse events in continuous administration, the incidence tended to be high in adverse events compared with the phase I/II study. But they were not particularly a significant one in terms of clinical management. The status of adverse events in readministration was not so different from that in the phase I/II study. There were no factors suggesting accumulative or delayed adverse events,

From the above, although the results requires a careful interpretation because of the small number of patients – 13 patients who received continuous administration or readministration in this study, JNJ-26866138 in continuous administration (long-term treatment) or readministration is expected to exert an antitumor effect and its safety profile is considered to show a good tolerability.

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