SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K., JAPAN
Name of Finished Product	doxorubicin HCl liposome injection, DOXIL
Name of Active Ingredient(s)	JNS002

Status: Approved
Date: 22 April2013
Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: JNS002-JPN-03

Title of Study: A Phase I Study of JNS002 (doxorubicin HCl liposome injection) in Combination with Bortezomib for Japanese Subjects with Relapsed or Refractory Multiple Myeloma

NCT No.: NCT01371227

Clinical Registry No.: CR018085

Study Center(s): Nagoya City University Hospital and Okayama Medical Center

Publication (Reference): none

Study Period: 09 May 2011 - 30 May 2012

Phase of Development: Phase 1

Objectives:

Primary objective of this study: To evaluate tolerability of the combination therapy of JNS002 and bortezomib in Japanese bortezomib-naïve patients with multiple myeloma who have ever received at least one line of chemotherapy (to evaluate the tolerability of the combination therapy of JNS002 and bortezomib at the approved foreign regimen).

Secondary objective of this study: To document the efficacy.

Methodology: A non-randomized, single-arm, open-label study.

Number of Subjects (planned and analyzed):

Initially, 3 subjects were enrolled and the incidence of dose limiting toxicity (DLT) was determined at the end of Cycle 1 to evaluate the study doses against the maximum tolerated dose (MTD). If the incidence was:

- = 3/3, then the study doses were estimated higher than the MTD. The study was discontinued without adding new patients.
- ≤2/3, additional 3 patients were enrolled to define the MTD. If the incidence in total is :

  (1) <2/6, the study doses were estimated lower than the MTD.

  (2) = 2/6, the study doses were estimated equal to the MTD.

  (3) ≥3/6, the study doses were estimated higher than the MTD.

This stepwise enrollment strategy allowed the evaluation of MTD in a safer manner than the enrollment of six patients in a row.

Diagnosis and Main Criteria for Inclusion: Three (3) to 6 subjects with multiple myeloma whose disease had either progressed after at least 1 line of prior therapy or was refractory to initial treatment were enrolled. Subjects who had previously received bortezomib, had received more than 240 mg/m^2 of doxorubicin, JNS002 (doxorubicin HCl liposome injection, DOXIL), or the equivalent amount of another anthracycline (i.e., 1 mg doxorubicin = 1 mg JNS002 = 1.8 mg epirubicin = 0.3 mg mitoxantrone = 0.25 mg idarubicin), or had a left ventricular ejection fraction less than the institution's lower limit of normal, were excluded.

Test Product, Dose and Mode of Administration, Batch No.: All subjects received combination treatment with JNS002 and bortezomib. The doses of JNS002 and bortezomib were 30 mg/m^2 and 1.3 mg/m^2, respectively.

Bortezomib 1.3 mg/m^2 by rapid (bolus) i.v. administration was given on Days 1, 4, 8, and 11 of each 21-day cycle. The Day 4, 8, and 11 doses could be delayed for up to 2 days to allow for platelet transfusions or other treatment requirements. However, doses of bortezomib should be at least 72 hours apart. In addition, JNS002 30 mg/m^2 by i.v. infusion was given at a rate of ≤ 1 mg/minute on Day 4 of every 21-day cycle after bortezomib. The i.v. catheter and tubing should be flushed with 5% glucose solution for infusion between administrations of the 2 drugs. Day 4 dosing of JNS002 could be delayed up to 48 hours as medically necessary. If an infusion reaction to JNS002 occurred, the infusion was stopped and after the symptoms resolved, administration of the remaining JNS002 at a rate of ≤ 0.75 mg/minute was attempted.

The amount (in mg) of JNS002 and bortezomib to be administered was determined by body surface area (BSA), which was calculated according to the standard nomogram used at each center. BSA was calculated on Day 1 of Cycle 1. If a subject experienced a greater than 10% change in weight from the weight used in the most recent BSA calculation, the subject's BSA should have been recalculated.

Duration of Treatment: Subjects received bortezomib 1.3 mg/m^2 as an i.v. bolus on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21). JNS002 30 mg/m^2 was given as an intravenous infusion at a rate of ≤1 mg/minute after bortezomib on Day 4 of each 21-day cycle. Treatment continued for a total of 6 cycles of therapy (126 days).

Criteria for Evaluation:

Safety Evaluations:

Safety endpoints included adverse events, laboratory tests (hematology, blood biochemistry, and urinalysis), pregnancy test, electrocardiogram (ECG), LVEF, chest X-ray, vital signs (body temperature, pulse rate, and blood pressure), and body weight.

Efficacy evaluations:

Preliminary efficacy evaluation was performed in terms of antitumor effect, according to criteria for assessment of antitumor effect similar to the European Group for Blood and Marrow Transplantation (EBMT) criteria.

Statistical Methods:

Safety Analysis

Subjects who received at least 1 administration of study agents were included in safety analyses.

All reported adverse events that newly occurred or worsened after first day of study agent until 30 days after last administration of study agent (i.e. treatment-emergent adverse events) were included in the analysis. The percentage of subjects with specific treatment-emergent adverse events was summarized.

Descriptive statistics were calculated for the change from baseline to each scheduled time point in clinical laboratory test results, vital sign measurements and weight. For ECG and chest X-ray, frequency distribution (presence or absence of abnormal finding) were presented.

Efficacy Analysis

Subjects who received at least 1 administration of study agents were included in efficacy analyses as Full Analysis Set (FAS). Individual data listings of anti-tumor effect using EBMT criteria, serum M-protein, urine M-protein, plasma cells in bone marrow aspirate/biopsy, lytic bone lesions, soft tissue plasmacytoma and corrected serum calcium were created.

RESULTS:

STUDY POPULATION:

- A total of 3 subjects were enrolled and received the study agents.
- The subjects were 65 years old or older. All subjects had more than 1 prior therapy
- The enrolled subjects discontinued the study prematurely in Cycle 2, 3, or 4. Two of the 3 subjects discontinued because of an adverse event, and the other subject discontinued because of a toxicity, which was not recovered within the protocol allowance, and treatment could not be continued.

EFFICACY RESULTS: The all enrolled subjects achieved PR.

SAFETY RESULTS:

- All subjects experienced Grade 3 or 4 treatment-emergent adverse events.
- All subjects experienced Grade 3 or 4 leukopenia, neutropenia, or thrombocytopenia. Grade 3 or 4 hematologic abnormalities were noted in all enrolled subjects during the study.
- No death was reported in this study. One SAE was reported.
- All subjects prematurely discontinued this study because of adverse events, and adverse events leading to discontinuation were all considered treatment-emergent.
- DLTs occurred in 3 of 3 subjects initially enrolled in this study. Two of 3 DLTs were Grade 4 thrombocytopenia, and one was Grade 3 ileus.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION(S): The tolerability of the combination therapy with JNS002 and bortezomib at the approved doses in foreign countries was not confirmed in Japanese subjects with relapsed or refractory multiple myeloma, under the protocol-specified conditions.

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