STATISTICAL ANALYSIS PLAN

ROLLOVER STUDY OF WEEKLY PACLITAXEL (BMS-181339) IN PATIENTS WITH ADVANCED BREAST CANCER

Protocol: CA139-387

NCT Number: NCT00971945

October 16, 2007 (Ver. 1.00)

[redacted]

Table of Contents

1 Introduction

The purpose of this document is to provide a detailed plan for the final analysis of rollover study of weekly Paclitaxel (BMS-181339) in patients with advanced breast cancer (Identification number: CA139-387).

Attached materials show the table format to be used in the statistical analysis report. These tables and figures are referenced in the analysis section. Each figures and tables show the dataset (Analysis Sets) used for the analysis.

[redacted]

3 Study Objectives

3.1 Primary Endpoint

The primary endpoint is the frequency and severity of adverse events (Subjective and objective findings and changes in laboratory (test) abnormalities) for the subjects in the study.

3.2 Secondary Endpoint

Tumor response and duration of response.

4 Study Overview

4.1 Study Design

This study is an extension study of weekly paclitaxel in subjects participating in the [redacted] who require continued weekly paclitaxel due to lack of alternative treatment, and is an open-label clinical study by enrollment using the central multicenter method.

The primary endpoint in this study will determine the frequency and severity of adverse events (Subjective and objective findings and changes in laboratory (test) abnormalities) in study subjects to evaluate the safety of continued paclitaxel treatment. In addition, the Safety Monitoring Board will be established as an advisory body to sponsor and the coordinating investigator to deliberate and report the preparation and revision of protocol, actions in the event of serious adverse event, and actions for situations requiring consideration of discontinuation of the entire study.

4.2 Study Population

Among patients with advanced/recurrent breast cancer who meet the inclusion criteria and participated in the [redacted], those who are judged by the investigator ([redacted]) to require continued administration of paclitaxel because there is no appropriate alternative therapy.

4.3 Dose, Route, and Duration of Study Drug

Paclitaxel 100 mg / m2 is intravenously infused for 1 hour after premedication,. The first dose date of paclitaxel is Day 1, and the drug is administered at Day 8, 15, 22, 29, 36 (7-day intervals (± 1 day)), and then the drug is withdrawn until Day 49. One course is 49 days, and in principle, one or more courses are administered. For subjects who do not meet the discontinuation criteria, administration should be continued as much as possible within the study period at the discretion of the investigator.

4.4 Blinding and Unblinding

Not applicable.

5 Criteria for Evaluation

5.1 Efficacy Evaluations

Tumor response will be assessed using the Breast Cancer Treatment Code (Edited by the Japan Breast Cancer Society). Response Evaluation Criteria in Solid Tumors (RECIST) will be evaluated for reference.

5.2 Safety Assessments

The safety endpoint will be adverse events (Subjective and objective findings and laboratory (test) abnormality), which will be graded according to the NCI Common Toxicity Criteria version 2 (JCOG Version). Final assessment of adverse events will be made by the Adjudication Committee for review outside the study site.

Toxicities not included in CTC will be graded in accordance with the following criteria as "Other" toxicity of the applicable category, with specific descriptions.

Grade 0: Normal, normal/within normal limits (WNL), none
Grade 1: Mild/mild toxicity
Grade 2: Moderate/moderate toxicity

Grade 3: Severe/severe toxicity
Grade 4: Life-threatening or toxicity leading to inactivity
Grade 5: Death due to toxicity

6 Sample Size Determination

The number of subjects with this study will be determined by the number of subjects continuing from the preceding [redacted] Currently, in Study [redacted], 9 subjects are continuing treatment, and therefore, it is expected that no more than 10 subjects will be enrolled in this study.

7 Interim Review

No interim analysis will be performed in this study; however, an interim analysis will be performed if necessary to support the application for approval.

8 Data Sets Analyzed

8.1 Enrolled Subjects

All subjects who are enroll to the study.

8.2 Treated subjects

Subjects who entered the study and received at least one dose of investigational product. Safety and efficacy analyses will be performed.

9 Statistical Analysis

This chapter is organized as follows.

9.1: Analysis Consideration

9.2: General methods

9.3 : Changes made to Statistical Analysis Described in the Protocol

9.4-9.7 : Detailed analysis method for analysis items.

(Presentation formats for each analysis is provided in the attachment.)

All analyses will be performed using SAS release 8.02.

9.1 Analysis Consideration

9.1.1 Subjects and Data Handling

Handling of subjects and data will be specified separately before data lock as needed.

9.1.2 Data conversion

No variables will be analyzed using converted values. However, this is not applicable to the case where an exploratory post-hoc analysis is performed.

9.1.3 Adverse Event Coding

Adverse event terms/names of diseases described in case report form were coded to MedDRA terms to be used for reporting of analysis results. The most recent or one previous MedDRA version at the time of analysis will be used.

9.1.4 Review of Subgroup

Subgroup will not be evaluated.

9.1.5 Covariate Alignment

Analyses that would require adjustment by covariate will not be performed.

9.1.6 Multicenter Test

Since the number of subjects per site is expected to be small, no investigation of inter-site differences will be conducted.

9.1.7 Multiplicity

Multiplicity is not applicable because no statistical test will be performed.

9.1.8 Significance Level

Significance level is not defined because no statistical test will be performed.

9.2 General Methods

Baseline should be the most recent measurement or finding up to the start of the first dose in the parent study.

Descriptive statistics will be used to summarize demographic factors, treatment status, and laboratory data. Categorical variables will be summarized using frequency tabulations.

Adverse events for which the causal relationship is "related", "Probably related" or "possibly related" are defined as events for which the relationship with investigational product cannot be ruled out (adverse drug reaction). Events assessed as "not likely relarted" or "not related" to the study drug should be assessed as not related to investigational product. The same adverse event may occur more than once within a subject's scope as a MedDRA SOC, HLGT, or PT, and will be counted only once in the adverse event summary table. If the same adverse event is regarded as a single event, the most abnormal grade among them will be used for summary. Similarly, if multiple same adverse events are counted as 1 event, the most abnormal grade among the related events will be used for summary. The same handling as above will be applied to the total number of subjects with adverse events.

For the outcome of adverse events, the final outcome by LLT in MedDRA is adopted as the outcome by PT in the order of priority of death > persistent > unknown > recovering > recovering, and the outcome in adverse drug reaction is handled in the same manner among related events.

When frequency tabulations are prepared for adverse events and laboratory (test) abnormalities changes by symptom name, they should be presented in ascending order of SOC (HLGT) codes and in descending order of the number of applicable subjects. If the number of subjects in the same, display them in ascending order of PT code.

The target of demographic analysis is data from the preceding study.

Dosing and efficacy analyses will be summarized, including data from the subject's previous study.

For the number of display digits to be used in the report, an appropriate number of digits should be selected according to the parameters, but rounding should be done as a rounded method unless otherwise specified. Proportion shows the first decimal places.

9.3 Changes made to Statistical Analysis described in the Protocol

9.3.1 Additional points

Tabulation of exposure was added.

9.3.2 Change

There were no changes.

9.4 Subject Disposition

9.4.1 Subject Disposition

Subject composition (Table 1.1)

- Study Drug administration
- Primary reason for discontinuation

One primary reason for discontinuation will be identified for each subject.

Reasons for discontinuation by discontinuation course (Table 1.2)

The discontinuation course is the sum of the administration courses in the preceding study.

9.4.2 Protocol Deviations

Protocol deviations (Table 1.3)

9.4.3 Baseline Subject Characteristics

Demographic characteristics (Table 2.1)

- Age (years)
- Body surface area (m^2)
- P.S. (ECOG)

The age should be accurately calculated from the date of informed consent and date of birth in years of age.

9.5 Drug Administration

9.5.1 Study Drug Administration

In the following summaries, the number of courses plus the number of courses administered in the preceding study will be used. (For example, if a subject completed or discontinued 2 courses of the parent study and subsequently entered an extension study, the first course of the extension study will be counted as 3 courses.)

Study Drug Administration (Table 3.1)

- Number of administration courses

– Number of dose
– Course interval (days)

・Course interval = first dose date in the course - last dose date in the previous course

Dose delay (Table 3.2)

Drug interruption (Table 3.3)

Dose reduction (Table 3.4)

9.6 Efficacy

9.6.1 Response, Duration of Response

In the following summary, the date will be specified based on the assessment by the attending physician and the data from the preceding study, and the period and cumulative dose will be calculated based on the date.

Duration of response (Japan Breast Cancer Society) (Table 4.1)

・Duration of CR response = date of progression - date of CR

・Duration of PR response = date of progression - date of PR

・Overall response duration= date of progression - date of first dose

The date of progression is defined as the earliest date among the date of progression of a lesion, the date of appearance of a new lesion, the date of initiation of subsequent treatment, or the date of death based on the evaluation criteria in the General Rules for Clinical Practice for Breast Cancer, and the date of the last measurement of a lesion in patients without progression.

Duration of response (RECIST) (Table 4.2)

・Duration of complete response = date of progression - date of CR

・Overall response duration = date of progression - date of PR

The date of progression is defined as the earliest date among the date of progression of lesion based on RECIST evaluation criteria, the date of appearance of new lesion, the date of initiation of subsequent treatment, or the date of death, and the date of the last measurement of lesion in patients without progression.

9.7 Safety

The following summaries are based on events that are new or ongoing in the extension study.

9.7.1 Subjective and objective adverse events

The number of subjects with subjective and objective adverse events will be summarized by SOC and PT. However, summaries by outcome will not be performed by SOC but only by PT.

Subjective and objective adverse events: by worst grade (Table 5.1)

Drug Related Subjective and objective adverse events: by worst grade (Table 5.2)

Drug Related Subjective and objective adverse events by outcome (Table 5.3)

9.7.2 Peripheral neuropathies

The number of subjects with peripheral neuropathy will be summarized by SOC and PT.

Peripheral nerve disorders: by worst grade (Table 5.4)

Peripheral nerve disorders- excluding "not related" and "not likely relarted" -: by worst grade (Table 5.5)

9.7.3 Nail Disorders

The number of subjects with nail disorders will be summarized by SOC and PT.

Nail disorders: by worst grade (Table 5.6)

9.7.4 Allergic Reactions

The number of subjects with allergic reactions will be summarized by SOC and PT. In addition, the occurrence by dexamethasone dose will be summarized.

Allergic reactions: by worst grade (Table 5.7)

9.7.5 Laboratory (Test) Abnormalities

For laboratory (test) abnormalities changes, the number of subjects with each HLGT and each PT will be summarized. However, summaries by outcome will not be performed by HLGT but only by PT.

Laboratory abnormalities: by worst grade (Table 6.1)

Laboratory abnormalities (Drug Related): by worst grade (Table 6.2)

Laboratory (test) abnormalities (Drug Related): Incidence by outcome (Table 6.3)

9.7.6 Laboratory Evaluations

9.7.6.1 Myelosuppression

Worst grade, nadir, number of days to nadir, and number of days to recovery of white blood cell count decreased (Table 6.4 a)

Worst grade of neutrophil count decreased, Nadir, number of days to Nadir, number of days to resolution (Table 6.4 b)

Nadir (lowest value), number of days to Nadir and number of days to resolution will only be calculated for subjects who achieve Grade ≥ 2 in each course. The calculation method is as follows:.

- Number of days to Nadir: date Nadir was reached - first dose date in each course + 1
- Recovery date: Between the day of achievement of Nadir and before the start of the next course (Last measurement time point including follow-up data in the last course), the first day when the grade has recovered to ≤ 1 and has not subsequently worsened to ≥ 2.
- Number of days to recovery: Recovery date - date Nadir was reached

10 List of Tables

The following figures and tables will be included in the analysis report:.

Table/table number	Title
Table 1.1	Subject Disposition
Table 1.2	Reason for Discontinuation by Discontinuation Course
Table 1.3	Protocol Deviations
Table 2.1	Demographic Characteristics
Table 3.1	Study Drug Administration - Including Prior Studies -
Table 3.2	Dose Delay - Including Prior Studies -
Table 3.3	Drug Interruption - Including Previous Studies -
Table 3.4	Dose Reduction - Including Previous Studies -
Table 4.1	Duration of Response (Japan Breast Cancer Society) - Including Prior Studies -
Table 4.2	Duration of Response (RECIST) - Including Prior Studies -
Table 5.1	Subjective and Objective Adverse Events
Table 5.2	Drug Related Subjective and Objective Events
Table 5.3	Drug Related Subjective and Objective Adverse Events by Outcome
Table 5.4	Peripheral Nerve Disorders
Table 5.5	Peripheral Neuropathies - excluding "not Related" "not Likely Related" -
Table 5.6	Nail Disorders
Table 5.7	Allergic Reactions
Table 6.1	Laboratory Test Abnormalities
Table 6.2	Laboratory Test Abnormalities (Drug Related)
Table 6.3	Laboratory Test Abnormalities (Drug Related) by Onset Status/Outcome
Table 6.4 a	White Blood Cell Count Decreased Recovered to ≤ Grade 1
Table 6.4 b	Neutrophil Count Decreased Recovered to ≤ Grade 1

[redacted]

Document History

Date	Edition Number	Person who created/updated	Remarks
2007/01/10	Draft	[redacted]	Initiation of draft preparation
2007/08/06	0.00	[redacted]	Completion of draft statistical analysis plan Submit to Reviewers
2007/09/07	0.50	[redacted]	Reflected the review results. Resubmission to Reviewers
2007/09/28	0.60	[redacted]	Reflected the results of the meeting with Clinical Strategy Department Resubmission to Reviewers
2007/10/16	1.00	[redacted]	Reflected the review results, and prepared the approval document.