A multicenter, retrospective, observation study to evaluate palbociclib plus letrozole for overall survival in Japanese subjects with HR-positive/HER2-negative advanced breast cancer

Protocol No.: A5481154

Statistical Analysis Plan

－Ver. 3.0－

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Preparation/revision records

<table>
<tr><td>Drug</td><td colspan="5">Palbociclib</td></tr>
<tr><td>Study title</td><td colspan="5">A multicenter, retrospective, observation study to evaluate palbociclib plus letrozole for overall survival in Japanese subjects with HR-positive/HER2-negative advanced breast cancer</td></tr>
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<tr><td rowspan="4">Preparation/revision records</td><td></td><td>Version No.</td><td>Date of preparation</td><td>Author</td><td>Revisions made</td></tr>
<tr><td>First version</td><td>Ver.1.0</td><td>12/25/2020</td><td>PPD</td><td>—</td></tr>
<tr><td rowspan="2">Revised version</td><td>Ver.2.0</td><td>3/1/2021</td><td>PPD</td><td>6.1.2 Descriptive Summary
Added the description on reverse Kaplan-Meier method.
7.2 Secondary Endpoints
Added the figure showing changes in subsequent treatment.
7.6 Overall Study Status
Added the description on the follow-up period estimation.</td></tr>
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Added the description on additional analyses.</td></tr>
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1 INTRODUCTION

This analysis plan describes data summaries and details of statistical analyses for the "multicenter, retrospective, observation study to evaluate palbociclib plus letrozole for overall survival in Japanese subjects with HR-positive/HER2-negative advanced breast cancer." Planned protocol outlines may be modified in this analysis plan; in which case, any changes made in the analytical methods or the definition of the primary endpoint shall also be reflected to the protocol.

2 STUDY OBJECTIVES

Primary Objective

To evaluate first-line palbociclib plus letrozole for overall survival (OS) in Japanese subjects with HR-positive/HER2-negative advanced breast cancer.

Secondary Objective

To investigate the types and duration of subsequent treatment following palbociclib plus letrozole therapy in Japanese subjects with HR-positive/HER2-negative advanced breast cancer.

3 STUDY DESIGN

This is a Japanese, multicenter, retrospective, observation study. This observation study is designed as a follow-up study to the Japanese phase 2 study of palbociclib (NCT01684215, the phase 2 part of Study A5481010; hereinafter, J-Ph2). In J-Ph2, 43 subjects were enrolled and 42 received palbociclib plus letrozole. Eight deaths were reported at the end of J-Ph2 (i.e., last subject last visit [LSLV], October 25, 2018). Of the remaining 34 subjects with no reported deaths, 4 refused further follow-up and 30 were being followed up for survival.

Medical charts of those 30 subjects in the post-J-Ph2 survival period will be used to retrospectively collect OS and subsequent-treatment data. For subjects transferred to another hospital, the investigator will be requested to make his/her utmost efforts to collect data from the hospitals to which the subjects were transferred. The investigator will complete paper-based case report forms (CRFs) at the start of the study at each site and during the annual reporting period specified by the sponsor. Subject IDs assigned in J-Ph2 will be used to collate the subject demographics and other relevant data between this observation study and J-Ph2 and to analyze the data.

Eight subjects with OS events confirmed in J-Ph2 and 4 who refused to continue follow-up after J-Ph2 will be analyzed based on data collected in J-Ph2.

3.1 Timing of analysis

In this study, data will be collected continuously until a sufficient number of OS events are available to determine the median OS. The number of OS events will be calculated for each annual reporting period; the primary endpoint will be analyzed only once.

4 DEFINITIONS OF ENDPOINTS AND BASELINE VARIABLES

4.1 Primary Endpoint

Overall survival (OS)

Defined as time from the date of the first dose of the investigational product in J-Ph2 to the date of any-cause death. Subjects whose death was unconfirmed will be censored at the last date of confirmed survival.

4.2 Secondary Endpoints

Overview of Subsequent Treatment

Subsequent treatment subject to data collection will be limited to systemic therapies prescribed by physicians for advanced breast cancer (chemotherapies, hormone therapies, molecular targeted drugs, etc.).

• Percentage of subjects by types of subsequent treatment (category: endocrine therapy-based, chemotherapy-based, others)
• Percentage of subjects by treatment line (category: no subsequent treatment, first subsequent treatment, second subsequent treatment)

Subsequent-treatment period

Defined as time from the start date to the end date of each line of treatment among subjects who received subsequent treatment. If "Ongoing" is checked for the latest record of an applicable subsequent treatment, data will be cut off at the date on which the CRF with "Ongoing" is fixed.

4.3 Other Endpoints

Clinical efficacy of subsequent treatment (categories: complete response, partial response, stable disease, progression, unknown)

• Percentage of subjects applicable to each category of clinical efficacy by each type of subsequent treatment
• Percentage of subjects applicable to each category of clinical efficacy by each treatment line

Time to start of chemotherapy

Defined as time from the date of the first dose of the investigational product in J-Ph2 to the date of the first subsequent chemotherapy or any-cause death, whichever occurred first. Surviving subjects who had not started subsequent chemotherapy will be censored at the last date of confirmed survival.

Dose Adjustment of Palbociclib

• Percentage of subjects by types of dose reduction (category: no dose reduction, dose reduction by 1 level to 100 mg, dose reduction by 2 levels to 75 mg, others)
• Percentage of subjects by reasons for dose reduction (category: adverse event, others) among those who reduced doses

Duration of Treatment with Palbociclib + Letrozole

The duration of treatment with palbociclib per dose (category: 125 mg, 100 mg, 75 mg, etc.) is defined as time from the date of the first dose to the end of treatment with the dose level.

The duration of treatment with letrozole is defined as time from the date of the first dose per investigational product in J-Ph2 to the date of the last dose of letrozole.

4.4 Key Baseline Variables

J-Ph2 database will be used for the following classification.
• ECOG PS
• Disease Free Interval since completion of prior therapy
• Prior Adjuvant Anticancer Treatment
• Disease Site (visceral, non-visceral)
• Disease Site (bone only, other)
• Age (<65, >=65)
• Dose Reduction Group
• Prior Chemotherapy
• Prior Endocrine Therapy
• Ki67 Status (<=20%, >20%)

5 ANALYSIS SET

The analysis set is a population of subjects who were enrolled in J-Ph2 and received the investigational product, excluding surviving subjects who did not give written or oral consent.

6 GENERAL HANDLING

6.1 Statistical Methods

6.1.1 Hypothesis

Not applicable

6.1.2 Descriptive Summary

Continuous variables will be calculated for descriptive statistics (the number of subjects, mean, standard deviation, median, minimum, and maximum), and categorical data will be calculated for the frequency and percentage (%).
Time-to-event data will be calculated for Kaplan-Meier estimates. Data will be plotted using the Kaplan-Meier methods, and as necessary the number of events and censored subjects will be tabulated. The event follow-up period will be estimated based on a reverse Kaplan-Meier method with which the Kaplan-Meier event/censoring indicator variables for the analysis of time to event data are inversely set out.

6.1.3 Confidence interval of time to event

The confidence interval of median time to event will be computed with a Brookmeyer and Crowley method using log-log transformation.

6.2 Day count

In principle, the day of the first dose of the investigational product in J-Ph2 will be defined as Day 1.

6.3 Handling of missing data

6.3.1 Missing dates

If the start or end day of subsequent treatment, the end day of palbociclib, or the end day of letrozole is missing, the “first day” will be imputed. Missing year or month will not be complemented.

6.4 Handling of Drug Data

Subsequent treatment will be classified based on the Prescription Drug Data File, Version 2020.10 or later. Classification by "types of subsequent treatment" is as specified in the attachment.

7 STATISTICAL ANALYSIS AND SUMMARY

7.1 Primary Endpoint

7.1.1 Overall survival (OS)

The data will be summarized using the Kaplan-Meier method and plotted on graphs. OS will be estimated for median and 95%CI.

7.1.2 Sensitivity analysis/supportive analysis for the primary endpoint

Not applicable

7.2 Secondary Endpoints

Percentage of subjects receiving subsequent treatment

The number and percentage of subjects will be calculated for treatment lines (First, Second) and types of subsequent treatment. Changes in subsequent treatment in subjects who proceeded to receive subsequent treatment will be summarized and plotted on graphs.

Subsequent-treatment period

Data for each treatment line will be summarized using a Kaplan-Meier method and plotted on graphs. The duration of subsequent-treatment period for each treatment line will be estimated for median and 95%CI. The same analyses will be performed for each type of subsequent treatment per treatment line.
The duration of all subsequent treatment will be plotted for each subject.

7.3 Other Endpoints

Clinical Efficacy of Subsequent Treatment

• Compute the percentage of subjects applicable to each category of clinical efficacy by each type of subsequent treatment.
• Compute the percentage of subjects applicable to each category of clinical efficacy by each treatment line.

The clinical efficacy of each and every subsequent treatment will be plotted for each subject along with the duration of the subsequent treatment.

Time to start of chemotherapy

The data will be summarized using the Kaplan-Meier method and plotted on graphs. The median time to start of chemotherapy and its 95%CI will be estimated.

Dose Adjustment of Palbociclib

• Compute the percentage of subjects applicable to each type of dose reduction.
• Compute the percentage of subjects applicable to each reason for dose reduction.

Duration of Treatment with Palbociclib + Letrozole

The duration of treatment with palbociclib + letrozole will be plotted for each subject. For palbociclib, the duration of treatment will be plotted by dose groups.

7.4 Subgroup Analyses

The same analysis described in "7.1 Primary Endpoint" will be performed for each category shown in "4.4 Major Baseline Variables" and for each category of the duration of palbociclib treatment (threshold: median, 24 months).

The following subgroup analyses will be performed based on the Kaplan-Meier method used for the Subsequent-treatment period (First Line) specified in 7.2 "Secondary Endpoints."
• Types of First Line
• Disease Site (visceral, non-visceral)

Plots for each subject in the subsequent-treatment period as per 7.2 "Secondary Endpoints" will be used to perform the following subgroup analyses.
• Disease Free Interval since completion of prior therapy
• Disease Site (visceral, non-visceral)
• Duration of treatment with palbociclib (threshold, median, 24 months)

The following subgroup analyses will be performed based on the Kaplan-Meier analyses for time to start of chemotherapy specified in 7.3 "Other Endpoints."
• Disease Free Interval since completion of prior therapy

• Disease Site (visceral, non-visceral)

7.5 Baseline Summary

Not applicable

7.6 Overall Study Status

The presence/absence of informed consent, the survival status, and the treatment status at the start/end of the study will be summarized along with the subject status at the end of the study. The study completion/discontinuation status and the reasons for study discontinuation among subjects who were receiving study treatment at the start of the study will be summarized.
Assessments of pre-existing and new lesions upon discontinuation of palbociclib and letrozole will be summarized along with data from J-Ph2.
The number of subjects with major protocol deviations will be listed.
The duration of survival follow-up will be estimated using a reverse Kaplan-Meier method.

7.7 Exposure to Study Treatment

Not applicable

7.8 Concomitant medications

Not applicable

7.9 Safety Endpoints

Not applicable

7.10 PK/PD Endpoints

Not applicable

8 REVISION HISTORY

See page 2.