Statistical Analysis Plan I3Y-MC-JPBM Addendum for Overall Survival Analyses

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

NCT02246621

Approval Date: 18-Sep-2017

1. Statistical Analysis Plan Addendum for Overall Survival Analyses:

I3Y-MC-JPBM: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting

Abemaciclib (LY2835219) Metastatic breast cancer

This study is a global, multicenter, double-blind, placebo-controlled, Phase 3 trial for women with hormone receptor positive, HER2 negative locoregionally recurrent or metastatic breast cancer randomized to receive nonsteroidal aromatase inhibitors with or without LY2835219.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I3Y-MC-JPBM
Phase 3

Statistical Analysis Plan Addendum 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 18-Sep-2017 GMT

2. Table of Contents

Section **Page**

3. Rationale for Addendum

This addendum is to document the changes in alpha spending of the overall analyses due to an unplanned overall survival (OS) analysis at the time of the 90-day safety update. The unplanned OS analysis is requested by the United States (US) Food and Drug Administration (FDA).

4. Analyses of Overall Survival

4.1. Background

Overall survival (OS) is an important secondary endpoint for this study. A gate-keeping strategy will be utilized to control the overall type I error at .025 (one-sided) for the secondary endpoint OS. That is, OS will be tested only if progression-free survival (PFS) is significant. More details concerning gatekeeping and alpha spending across multiple analyses of OS are provided in the I3Y-MC-JPBM Statistical Analysis Plan (SAP) Version 5 Section 6.7.3.

4.2. Definition

The OS time is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date.

4.3. Hypotheses and Analysis

Letting $S_A(t)$ and $S_P(t)$ denote the OS functions of abemaciclib + nonsteroidal aromatase inhibitor (NSAI) and placebo + NSAI respectively, the null hypothesis

$$H_0: S_A(t) = S_P(t), i=0,1,$$

will be tested against the one-sided alternative hypothesis

$$H_1: S_A(t) > S_P(t), i=0,1,$$

where i=0 represents the hypothesis in the visceral disease population (VIS) and i=1 represents the hypothesis in the intent-to-treat population (ITT).

There are 5 interim analyses and 1 final analysis to test the null hypotheses which will occur at the following time points:

- The first interim PFS analysis (189 PFS events)
- 90-day safety update (data cutoff of 11 August 2017)
- The final PFS analysis (240 PFS events)
- Approximately 189 OS events
- Approximately 252 OS events
- Final OS analysis: At least 315 OS events in the ITT and at least 189 events in the VIS.

To maintain the experiment-wise type I error rate, OS will be hierarchically tested in the following way: only if the test of PFS is significant will OS also be tested inferentially for significance (Glimm et al. 2010); specifically:

- The first potential time point for OS analysis will be at the time of the PFS interim analysis. If PFS is significant at this stage, the first analysis of OS will also be performed. If OS is not significant at this stage, the second analysis of OS will be performed at the time of the 90-day safety update. If OS is not significant at this stage, a third analysis of OS will be performed at the final analysis of PFS (240 PFS events). If the OS is not significant at this stage, an interim analysis of OS will be performed after approximately 189 deaths have been recorded. If the OS is not significant at this stage, an interim analysis of OS will be performed after approximately 252 deaths have been recorded. If OS is not significant at this stage, a final analysis of OS will be performed after at least 315 deaths in the ITT and at least 189 events in the VIS.
- If PFS is not significant at the time of the interim analysis of PFS but is significant at the final analysis for PFS, the second analysis of OS will be performed. In terms of alpha spending, this analysis will be performed as if the first analysis of OS had occurred at the interim PFS analysis (Glimm et al. 2010). If OS is not significant at this stage, the next analysis on OS will be performed at the time of the 90-day safety update. If the OS is not significant at this stage, an interim analysis of OS will be performed after approximately 189 deaths have been recorded. If the OS is not significant at this stage, an interim analysis of OS will be performed after approximately 252 deaths have been recorded. If OS is not significant at this stage, a final analysis will be performed after at least 315 deaths in the ITT and at least 189 deaths in the VIS.
- If PFS is not significant after either the interim PFS analysis or the final PFS analysis, OS will not be statistically evaluated.

At each analysis, the hypotheses above will be tested using a one-sided stratified log rank test, stratified by nature of disease and prior (neo)adjuvant endocrine therapy for the ITT, and stratified by prior (neo)adjuvant endocrine therapy for the VIS.

Following a positive PFS result, the one-sided alpha of .025 will be allocated between the VIS and ITT using a graphical approach, with an initial allocation of .005 for the VIS and .020 for the ITT. The cumulative one-sided type I error rate within each population will be maintained using the Lan-Demets method. Specifically, an alpha-spending function corresponding to the following O'Brien-Fleming type stopping boundary will be used for these interim analyses:

$$\alpha^{*}(t_k) = 2\left(1 - \Phi\left(\Phi^{-1}(1-\alpha/2) \Big/ \sqrt{t_k}\right)\right).$$

Here, t_k is the information fraction at time k, Φ is the standard normal cumulative distribution function, and Φ^{-1} is the standard normal quantile function.

The total alpha to be allocated by the alpha-spending function for each hypothesis is based on the alpha at each node of the graph from JPBM SAP Version 5 Figure JPBM.6.1 at the time of analysis. The alpha levels will be adjusted according to the rejection history and the

alpha-spending functions based on observed number of events using software that implements this alpha-spending function (for example, ADDPLAN 6.0 or SAS 9.2, or East 6.0).

5. References

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. *Stat Med*. 2010;29(2):219-228.

Leo Document ID = 1641b92a-fe25-4b14-b269-c76e5351b4c5

Approver: [redacted]
Approval Date & Time: 18-Sep-2017 13:21:04 GMT
Signature meaning: Approved