

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

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without LY2835219, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

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**1. Statistical Analysis Plan Addendum for Overall Survival Analyses:**

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**Abemaciclib (LY2835219)**

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

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### **3. Rational for addendum**

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

## 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 0.025 (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 JPBL SAP v4 Section 6.7.3.3.

### 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 cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cut-off date.

### 4.3. Hypotheses and Analysis

Letting  $S_A(t)$  and  $S_P(t)$  denote the overall survival functions of abemaciclib + fulvestrant and placebo + fulvestrant respectively, the null hypothesis

$$H_0: S_A(t) = S_P(t)$$

will be tested against the 1-sided alternative hypothesis

$$H_1: S_A(t) > S_P(t).$$

There are 4 interim analyses and 1 final analysis to test the null hypotheses which will occur at the following time points:

- The first interim PFS analysis (265 PFS events)
- The final PFS analysis (378 PFS events)
- 90 day safety update (data cut-off of 05May2017)
- 331 OS events
- Final OS analysis: 441 OS events

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 final analysis of PFS (378 PFS events). If OS is not significant at this stage, a third analysis of 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 331 deaths have been recorded. If OS is not significant at this stage, a final analysis of OS will be performed after approximately 441 deaths have been recorded.

- 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 90 day safety update. If the OS is not significant at this stage, an interim analysis of OS will be performed after approximately 331 deaths have been recorded. If OS is not significant at this stage, a final analysis will be performed after approximately 441 deaths have been recorded.
- 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 null hypothesis above will be tested using a 1-sided stratified log rank test, stratified by nature of disease and prior sensitivity to endocrine therapy.

The cumulative 1-sided type I error rate of .025 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 this interim efficacy analysis:

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

Here,  $t_k$  is the information fraction at time  $k$ ,  $\Phi$  is the standard normal cumulative distribution function, and  $\Phi^{-1}$  is the standard normal quantile function. The boundary p-value at each analysis will be calculated based on the actual number of events observed at the time of analysis using software that implements this alpha-spending function (for example, ADDPLAN 6.0 or SAS 9.2, or East 6.0).

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