I3Y-MC-JPCG Statistical Analysis Plan Version 1

A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

NCT02747004

Approval Date: 29-Jun-2016

1. Statistical Analysis Plan: I3Y-MC-JPCG: A Randomized, Open-Label, Phase 2 Study of Abemaciclib plus Tamoxifen or Abemaciclib Alone, in Women with Previously Treated Hormone Receptor-Positive, HER2-Negative, Metastatic Breast Cancer

Abemaciclib (LY2835219) Metastatic breast cancer

Study I3Y-MC-JPCG is a Phase 2, randomized, open-label study of abemaciclib plus tamoxifen or abemaciclib alone, in women with previously treated hormone receptor-positive, HER2-negative, metastatic breast cancer.

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Protocol I3Y-MC-JPCG
Phase 2

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

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a subject received study drug or any other protocol intervention.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the efficacy, in terms of progression-free survival (PFS), in patients with metastatic breast cancer (mBC) of abemaciclib 150 mg every 12 hours (Q12H) plus tamoxifen (Arm A), abemaciclib 150 mg Q12H (Arm B), and abemaciclib 200 mg Q12H plus primary prophylactic loperamide (Arm C).

4.2. Secondary Objectives

The secondary objectives of the study are the following:

- To evaluate the efficacy of abemaciclib, monotherapy and in combination with tamoxifen, in terms of objective response rate (ORR), duration of response (DoR), and overall survival (OS)

- To assess the safety profile of abemaciclib monotherapy and in combination with tamoxifen

- To characterize the pharmacokinetics (PK) of abemaciclib and its metabolites; in addition to tamoxifen and its active metabolite endoxifen

- To compare self-reported pain, pain interference, symptom burden, health status, and overall quality of life

4.3. Exploratory Objectives

The exploratory objectives of the study are the following:

- To evaluate the associations between biomarkers and clinical outcomes

- To evaluate the relationship between abemaciclib and tamoxifen exposure and response

5.   Study Design

5.1.   Summary of Study Design

Study I3Y-MC-JPCG (JPCG) is a Phase 2 multicenter, randomized, open-label trial in patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) mBC who have progressed on or after prior endocrine therapy and have received prior treatment with at least 2 chemotherapy regimens, of which at least 1 but no more than 2 regimens should have been administered in the metastatic setting.

Figure JPCG.1 illustrates the study design.
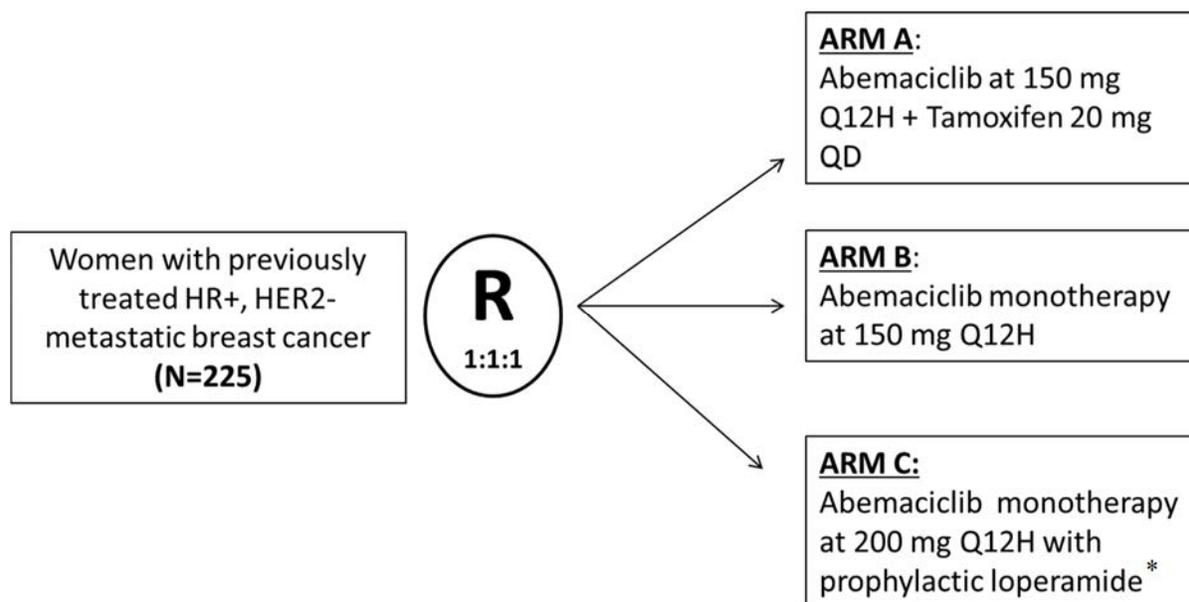
Abbreviations: HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; Q12H = every 12 hours; QD= every day; R = randomization.
* For Arm C only. During Cycle 1, prophylactic loperamide (2 mg) will be administered orally with each dose of abemaciclib. During Cycle 2 and beyond, loperamide will be administered at investigator's discretion and/or if clinically indicated.

Figure JPCG.1.   Illustration of study design.

5.2.   Determination of Sample Size

The primary objective of PFS will be tested at an experiment-wise one-sided alpha level of .10. Assuming a hazard ratio (HR) of .667 for Arm A compared to Arm C (corresponding to an increase in median PFS from approximately 6 months to 9 months), approximately 110 events across the 2 arms are required to achieve approximately 80% power (165 events across all 3 arms). Assuming 30% censoring, 75 patients per arm will be enrolled (225 patients total).

The informal noninferiority rule for comparing Arm B to Arm C is as follows: if the observed PFS HR is less than 1.2, Arm B will be considered noninferior to Arm C. Assuming 110 events

across the 2 arms, this design provides 80% probability to show the PFS HR is less than 1.2, assuming a true HR = 1.

The study will enroll approximately 225 patients in a 1:1:1 randomization (approximately 75 patients per treatment arm for women with previously treated HR+, HER2- mBC).

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned to Arm A, Arm B, or Arm C.

Approximately 225 patients will be randomized in a 1:1:1 ratio. Randomization will be stratified by the presence of liver metastases (yes versus no) and prior tamoxifen therapy in the advanced/metastatic setting (yes versus no).

The interactive web-response system (IWRS) will use randomization factors to assign study treatment to each patient.

6. A Priori Statistical Methods

6.1. General Considerations

6.1.1. Populations

The following populations will be defined for this study:

Entered population: will include all patients who sign the informed consent document. This population will be used for disposition summaries.

Enrolled or intention-to-treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

Safety or randomized and treated population: will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all randomized patients who received at least 1 dose of study treatment and have at least 1 postbaseline evaluable PK sample.

Biomarker population: will include all randomized patients with evaluable baseline blood, plasma, or tissue samples. Patients with postbaseline samples will be a subset of this defined biomarker population.

6.1.2. Definitions and Conventions

Study drug refers to abemaciclib.

Study treatment refers to abemaciclib plus tamoxifen or abemaciclib.

The **date of randomization** is the date the patient was randomly assigned to Arm A, Arm B, or Arm C using the IWRS.

The **date of first dose** is the date of the first dose of abemaciclib or tamoxifen.

The **baseline value of a safety assessment** is the last value observed prior to the first dose of abemaciclib or tamoxifen.

The **baseline value of an efficacy assessment** is the last value observed prior to the date of randomization. If a patient's first assessment occurs after randomization but prior to the first dose, this assessment will be used as the baseline.

The **study day of a safety event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if

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an event occurs on 08JUN2016 and the date of first dose was 06JUN2016, the study day of the event is 3.

- the difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05JUN2016 and the date of first dose was 06JUN2016, the study day of the event is -1.

The **study day of an efficacy event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of randomization plus 1 for all events or assessments occurring on or after the date of randomization.

- the difference between the date of the event or assessment and the date of randomization for all events or assessments occurring before the date of randomization.

One month is defined as 365/12 days.

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all confidence intervals (CIs) will be given at a 2-sided 95% level. The primary objective of PFS will be tested at an experiment-wise one-sided alpha level of .10.

6.2. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant section.

6.3. Patient Disposition

The number and percentage of patients entered into the study, enrolled in the study, and treated as well as reasons for discontinuation from study treatment and reasons for discontinuation from study will be summarized by treatment arm. A listing of patient disposition will be provided.

6.4. Patient Characteristics

6.4.1. Demographics

Patient demographics will be summarized for all enrolled patients. Patient demographics will include sex, race, ethnicity, country, age, height, weight, and body mass index.

6.4.2. Baseline Disease Characteristics

Disease characteristics will be summarized. Disease characteristics will include the following:

- study entry diagnosis

- disease extent at study entry (metastatic recurrent disease versus locally advanced recurrent disease)

- nature of disease (visceral metastases or other)

- number of organs involved (1, 2, or 3+)

- metastatic site(s)

- estrogen receptor status

- progesterone receptor status

- baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS)

Nature of disease and number of organs involved will be derived from the 'Target Tumor Identification and Results' and 'Non-Target Tumor Identification and Results' electronic clinical (case) report forms (eCRFs) at baseline. The number of organs involved will be derived from the location codes of the target and non-target lesions.

6.4.3. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA ™]) will be summarized.

6.4.4. Prior Therapies

Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by type of regimen (endocrine therapy, chemotherapy, targeted therapy, or other) and reason for regimen ([neo]adjuvant therapy or therapy for locally advanced or metastatic disease). Frequency of each specific therapy will be tabulated within each type of regimen and reason for regimen.

Most recent systemic therapy and the duration of that therapy will be summarized. This summary will include median duration of treatment (date of end of therapy – date of start of therapy + 1) and frequency of each category of therapy. If only the month and year of a treatment date or progression date is available, the day will be imputed to the 15th.

6.4.5. Poststudy Treatment Discontinuation Therapies

Therapies received following study treatment discontinuation will be summarized by arm.

Therapies will be summarized overall and by category: endocrine therapy, targeted therapy, or chemotherapy.

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6.5. Treatment Compliance

Treatment compliance of abemaciclib will be measured by pill counts and summarized. Compliance will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld for medical or logistical reasons). The total assigned dose for a patient in Arm A or B with no adjustments or omissions is 150 mg per dose × 2 doses per day × 28 days = 8400 mg. The total assigned dose for a patient in Arm C with no adjustments or omissions is 200 mg per dose × 2 doses per day × 28 days = 11200 mg.

Dosing information for tamoxifen (Arm A) will be collected at each cycle/visit. Dosing information for prophylactic loperamide (Arm C) will be collected at Cycle 1.

6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be summarized by number and percentage of patients for the safety population using the base name (without esters or salts).

6.7. Efficacy Analyses

Unless otherwise noted, all efficacy analyses will be performed on the ITT population.

The stratification factors for the analysis of primary and secondary analyses are presence of liver metastases (yes versus no) and prior use of tamoxifen in the advanced/metastatic setting (yes versus no). The stratification factors are captured in the IWRS and are also derived from information collected on eCRFs. Unless otherwise specified, all stratified analyses will be based on the stratification factor per eCRFs. A cross tabulation of the frequency of each level of the stratification factor per IWRS and eCRF will be produced.

Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all CIs will be given at a 2-sided 95% level. The primary objective of PFS and secondary objective of OS will be tested at an experiment-wise one-sided alpha level of .10.

6.7.1. Primary Outcome and Methodology

The primary endpoint of this study is PFS. PFS time is measured from the date of randomization to the date of investigator-determined objective progression as defined by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST v1.1), or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no postinitiation (that is, postbaseline) radiographic assessment is available. The detailed censoring rules are described in Table JPCG.6.1.

Table JPCG.6.1. **PFS Event/Censoring Scheme**

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate postbaseline radiological tumor assessment available and death reported after 2 scan intervals following randomization[b]	Censored	Date of randomization
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of randomization (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)[b]	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

[a] Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

[b] Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

Since radiologic imaging is required every 8 weeks (-7 days) from the first dose of study therapy, 2 scan intervals will be considered as 112 days.

There is one planned primary analysis for PFS in this study, which will be performed after 110 events have been observed in Arms A and C of the ITT population based on investigator assessment. The PFS analysis to test the superiority of abemaciclib plus tamoxifen (Arm A) to abemaciclib plus prophylactic loperamide (Arm C) in improving PFS time will be performed on the ITT population at an experiment-wise one-sided alpha level of .10 and will use the log-rank test stratified by the presence of liver metastases and prior use of tamoxifen in the advanced/metastatic setting.

6.7.2. Additional Analyses of the Primary Outcome

6.7.2.1. Progression-Free Survival Curves and Hazard Ratio

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at 3, 6, 9, and 12 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

The corresponding HR between Arms A and C will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. An additional unstratified

Cox regression model will be employed to explore the effects of the stratification variables on treatment response.

Arm B (abemaciclib 150 mg) will be compared against Arm C (abemaciclib 200 mg + prophylactic loperamide) in an informal manner. If the PFS HR is less than 1.2, Arm B will be considered noninferior to Arm C ("informal Phase 2 non-inferiority"). This comparison will use the same methodology described above. Arm A will not be compared against Arm B using a log-rank test or Cox HR model, but the Kaplan-Meier estimates for Arms A and B will be available from the previous analyses.

6.7.2.2. Restricted Mean Difference

The common method for describing benefit on the time scale is to calculate the difference in median event time between the 2 treatment arms. An alternative method for describing benefit on the time scale is to estimate the average difference between the Kaplan-Meier (KM) curves. This corresponds to calculating the difference in the average time to event for the 2 treatment arms (Irwin 1949; Karrison 1997; Meier et al. 2004). Similar to the HR, this method uses all of the available information across the KM curves, but has the additional advantage of assessing benefit on the time scale.

To estimate an improvement in PFS with abemaciclib plus tamoxifen compared to abemaciclib alone, we will follow the method of Irwin (1949) detailed in Karrison (1997) and Meier (2004) for estimating the 'difference in average PFS', which we will refer to more formally as the restricted mean difference in PFS.

The area under each KM curve will be calculated using numerical integration (trapezium rule) per Karrison and implemented in SAS using PROC LIFETEST. The difference between treatment arms and a CI for the difference will be formed.

Since the KM curve may be ill-determined beyond a certain range, or even undefined (if the longest observation is censored), for evaluation and comparison of means, the area under each KM curve will be calculated between time 0 and restriction time T, which is why this is referred to as a "restricted mean". Following the suggestion of Karrison, the restriction time T will be chosen as largest time point t such that the standard error (SE) of the survival estimate at time t in each treatment group is no more than 0.075. For this purpose, we will use the simple, albeit conservative, formula proposed by Peto et al. (1977) for calculating the SE of S(t) as $SE\big(S(t)\big) = S(t)\sqrt{\big(1 - S(t)\big)/n(t)}$, where n(t) is the number of patients still at risk at time t.

6.7.3. Secondary Efficacy Analyses

6.7.3.1. Objective Response Rate

Objective response rate (ORR), disease control rate (DCR), and clinical benefit rate are summary measures of best overall response (BOR) as defined by RECIST v1.1. BOR is derived from time point responses. All time point responses observed while on study treatment and during the short-term follow-up period (but before the initiation of postdiscontinuation therapy) will be included in the derivation.

Each patient's BOR will be categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). Patients with SD will be further classified as SD ≥6 months or SD <6 months. Stable disease ≥6 months includes all patients with a best response of SD and a PFS time of ≥6 months. A BOR of CR or PR will not require confirmation.

Objective response rate is the proportion of patients with a BOR of CR or PR. Clinical benefit rate is the proportion of patients with a BOR of CR or PR, or SD ≥6 months. Disease control rate is the proportion of patients with a BOR of CR, PR, or SD.

For each of these rates, point estimates and CIs (using the normal approximation to the binomial) will be calculated by treatment arm. Stratified tests comparing these rates between treatment arms will be conducted using a Cochran-Mantel-Haenszel test.

6.7.3.2. Duration of Response

The DoR time is defined only for responders (patients with a BOR of CR or PR). It is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. It is calculated as date of progression or death − date of first response evaluation of CR or PR + 1. The DoR will be censored according to the same rules as PFS.

A KM analysis of DoR will be performed to estimate the DoR curve for each arm. Point estimates and CIs for DoR quartiles and DoR rates will be calculated every 3 months for the first 12 months.

6.7.3.3. Overall Survival

Overall survival is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. The first OS analysis will be at the time of the PFS analysis. The final analysis of OS will occur 24 months after the last patient enters treatment.

The OS analysis to test the superiority of abemaciclib plus tamoxifen to abemaciclib plus prophylactic loperamide in improving OS time will use the log-rank test stratified by the presence of liver metastases and prior use of tamoxifen in the advanced/metastatic setting.

The following additional analyses will be conducted for OS:

- Kaplan-Meier curves (Kaplan and Meier 1958) will be generated; medians, quartiles, and appropriate point probabilities will be calculated. Interval estimates will be calculated at every 6 months up to 24 months.
- The Cox regression stratified by the randomization factors (Cox 1972) will be used to estimate the HR between the Arm A and Arm C treatment groups, along with CI.

6.8. Health Outcomes/Quality-of-Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- mBPI-sf (modified Brief Pain Inventory, Short Form)

- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30)

Descriptive statistics will be calculated for patient-reported data for each instrument. The number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument, including the reason not completed.

Change from baseline at time point = score at time point – baseline score.

Maximum postbaseline score = maximum of postbaseline score measured across all time points while on treatment.

Maximum increase from baseline = maximum postbaseline score – baseline score.

Exploratory analysis may be performed to investigate associations between patient-reported data (mBPI-sf and EORTC QLQ-C30) and additional clinical, efficacy, and /or utilization measures as appropriate.

6.8.1.1. Pain Assessment

Individual pain items on the mBPI-sf (that is, worst, least, average, and current pain) will be described using descriptive statistics by treatment arm and cycle. A mixed effects, repeated measures model will be applied to compare treatment arms by cycle with respect to change from baseline for each item. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized. The analysis will include all cycles for which at least 25% of patients in each arm have an mBPI-sf assessment.

Corresponding analyses will also be conducted for the mean of 7 pain interference with function items. If a patient does not complete Questions 5a through 5g on the mBPI-sf, the mean score for the 7 pain interference items will be calculated based on those answered questions when at least 4 out of 7 questions were completed (that is, ≥50% of the questions were answered).

Pain analysis will be based on all enrolled patients with at least 1 baseline and 1 postbaseline score when change from baseline is analyzed.

6.8.1.2. Health-Related Quality of Life

EORTC QLQ-C30 instrument data will be scored as described by Aaronson and colleagues (Aaronson et al. 1993), yielding scores for a global health status scale, 5 functional scales, and 9 symptom scales. Descriptive statistics for each EORTC QLQ-C30 scale will be calculated. A mixed effects, repeated measures model will be applied to compare treatment arms by cycle with respect to change from baseline for each scale. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized. The analysis will include all cycles for which at least 25% of patients in each arm have an assessment.

6.9. Utilization

Utilization data will be summarized by category across arms. The following categories will be described:

- analgesics (on study treatment and during short-term follow-up)

- antidiarrheal therapy (on study treatment and during short-term follow-up)

- transfusions (on study treatment and during short-term follow-up)

- hospitalizations (on study treatment and during short-term follow-up)

- postdiscontinuation surgery, radiotherapy, and systemic therapy.

For categorical variables, frequency and the corresponding proportions will be calculated. Continuous variables (days of hospitalization) will be described by the mean, median, and standard deviation.

6.10. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic and pharmacodynamic analyses will be performed according to a separate PK analysis plan.

6.11. Safety Analyses

6.11.1. Extent of Exposure

Drug exposure, dose intensity, and drug adjustment (dose omissions and reductions) for abemaciclib, tamoxifen (Arm A) and primary prophylactic loperamide (Arm C, Cycle 1) will be summarized for all treated patients per treatment arm. Drug exposure will include summaries of cycles received per patient, duration on therapy, and cumulative dose. Dose intensity will be calculated as the actual cumulative amount of drug taken divided by the duration of treatment. Relative dose intensity will be calculated as the actual amount of drug taken divided by the amount of drug prescribed times 100% (that is, expressed as a percentage). The summary of dose adjustments and omissions will include the reason for adjustment or omission.

For abemaciclib and tamoxifen, extent of exposure will be measured by pill counts. Dose intensity will be expressed in mg/day. The assigned cumulative dose for abemaciclib while on study is 2 doses per day × 150 mg per dose × number of days on treatment for Arms A and B. The assigned cumulative dose for abemaciclib while on study is 2 doses per day × 200 mg per dose × number of days on treatment for Arm C. For Arm A, the assigned cumulative dose for tamoxifen while on study is 1 dose per day × 20 mg per dose × number of days on treatment. For Arm C, during Cycle 1, the assigned cumulative dose for prophylactic loperamide is 2 doses per day x 2 mg per dose × number of days on treatment.

6.11.2. Adverse Events

Adverse event (AE) terms and severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 4. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA. Adverse events will be reported using the following reporting process:

- In CTCAE Version 4, each CTCAE term is a MedDRA lower level term (LLT), except in the case where the CTCAE term is a MedDRA System Organ Class (SOC) followed by 'Other – specify'.

- The CTCAE Version 4 term reported by the investigator will be mapped to the MedDRA PT and SOC of the corresponding MedDRA LLT, unless the reported CTCAE term is 'Other – specify'.

- If the reported CTCAE term is 'Other – specify' the MedDRA LLT, PT, and SOC mapped from the verbatim AE term will be used.

- All listings and summaries will use the PT resulting from this process.

Preexisting conditions are defined as AEs that begin prior to the first dose of study drug.

- A treatment-emergent adverse event (TEAE) is defined as any AE that begins between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any preexisting condition that increases in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment).

Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

A serious adverse event (SAE) is any AE during this study that results in one of the following outcomes:

- death

- initial or prolonged inpatient hospitalization

- a life-threatening experience (that is, immediate risk of dying)

- persistent or significant disability/incapacity

- congenital anomaly/birth defect

- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following summaries and listings will be produced:

- Overview of AEs

- Summary of TEAEs by PT (any grade and Grade ≥ 3)

- Summary of TEAEs by SOC and PT (any grade and Grade ≥ 3)

- Summary of TEAEs by SOC and PT and maximum grade (1-5)

- Summary of treatment-emergent SAEs by SOC and PT (any grade and Grade ≥ 3)

- Summary of AEs as reason for study treatment discontinuation by SOC and PT

- Listing of SAEs

The TEAE and SAE summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment, where relationship of the AE to the study treatment will be assessed by the investigator (yes or no).

Diarrhea, nausea, and vomiting are listed as adverse drug reactions in the abemaciclib Investigator's Brochure. To evaluate the effect of prophylactic loperamide added to abemaciclib monotherapy given at 200 mg Q12H, the rates of gastrointestinal toxicities between Arm C of Study JPCG and the enrolled population of Study I3Y-MC-JPBN (MONARCH 1) will be compared.

6.11.3. Deaths, Other Serious Adverse Events

A summary of all deaths, including reasons for deaths, will be provided. All deaths, deaths on therapy, deaths within 30 days of discontinuation of study therapy, deaths on therapy or within 30 days of discontinuation of study therapy, and deaths after 30 days of discontinuation of study therapy will be summarized by reason for death. For deaths due to AE, the preferred term will be provided. In addition to the tabular summary, a by-patient listing of all deaths on study not attributed to study disease by the investigator will be provided.

6.11.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE Version 4. These calculated grades will be summarized by cycle and maximum postbaseline grade over the entire study for each treatment arm. Treatment-emergent changes will be summarized by the maximum postbaseline grade, and a shift table of baseline grade by maximum postbaseline grade will be produced.

6.11.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight, and ECOG PS will be summarized by cycle.

6.11.6. Electrocardiograms

Local electrocardiograms (ECGs) are scheduled to be performed only at baseline. A listing of ECG findings at baseline and unscheduled postbaseline visits that are considered to be a medical history condition or an AE will be provided.

6.12. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for each of following potential prognostic subgroup variables:

- Baseline stratification factors (presence of liver metastases and prior use of tamoxifen in the advanced/metastatic setting)

- Disease setting (metastatic versus locally advanced recurrent)

- Nature of disease (visceral or other)

- Number of organs involved (1 versus 2 versus 3+)

- Age (<65 years versus ≥65 years)

- Progesterone receptor status (positive versus negative)

- Baseline ECOG PS (0 versus 1)

If a level of a factor consists of fewer than 33% of randomized patients (corresponding to 25 patients per arm), analysis within that level will be omitted.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed. Estimated HRs and CIs for the within-subgroup analyses will be presented as a Forest plot along with p-values for tests of interactions between subgroup variables and treatment.

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

6.13. Protocol Violations

Significant protocol violations that potentially compromise the data integrity and patients' safety will be summarized by treatment group for all randomized patients. These violations will include deviations that can be identified programmatically and those that can only be identified by the clinical research associate during monitoring. Significant protocol deviations are described in another document within the study Trial Master File.

6.14. Interim Analyses and Data Monitoring

There are no planned interim analyses prior to the primary analysis of PFS.

6.15. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report and Investigator's Brochure analyses, are described in the LY2835219 Program SAP.

6.16. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:

  o the number of participants at risk of an event

- o   the number of participants who experienced each event term

- o   the number of events experienced

- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

- AE reporting is consistent with other document disclosures for example, the clinical study report, manuscripts, and so forth.

7. References

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