Protocol A5481126

Prospective, multicenter, observational study to evaluate patient-reported outcome and physical activity using smartphone-based application and wearable device in Japanese patients with HR+/HER2- advanced breast cancer treated with palbociclib plus endocrine therapy or endocrine monotherapy

Statistical Analysis Plan (SAP)

Version: **1.1**

Date: **April 4, 2023**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1.0 (29 Mar 2021)	Amendment 1 (01 Sep 2020)	N/A	N/A
Version 1.1 April 4, 2023			Detailed the definition of the baseline values [6.1.1.1, 6.1.2.1.] Added the endpoints and secondary analyses; scores of EORTC-QLQ-C30 and physical activity metrics.[3.1., 6.1.1.2., 6.1.2.2.] Added week as the covariate of the mixed-model.[6.1.2.1.] Modify the filter of the physical activity metrics (minutes with "~~WAKE~~ FILTERED") [3.1. Physical activity metrics (Sedentary time)] Detailed the definition of the subset analyses [6.4.] add the variables for the subset analyses[6.4.]

2. INTRODUCTION

Palbociclib is a selective, oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that prevents cell proliferation by blocking cell cycle progression from the G1 to the S phase. In Japan, palbociclib was approved in 2017 for the treatment of HR+/HER2- inoperable or recurrent breast cancer. The safety and efficacy of palbociclib were investigated in two phase 3, randomized, double-blind, placebo-controlled, multicenter trials (PALOMA-2 and PALOMA-3).

PALOMA-2 demonstrated that median progression-free survival (PFS) was 24.8 months with palbociclib + letrozole and 14.5 months with placebo + letrozole (hazard ratio=0.58 [95% CI, 0.46-0.72] P<0.000001) as initial therapy for postmenopausal women with ER+/HER2- ABC. In Japanese subgroup analysis in PALOMA-2, median PFS was 22.2 months with palbociclib + letrozole vs 13.8 months with placebo + letrozole (hazard ratio=0.59 [95% CI, 0.26-1.34]).

Common adverse events (AEs; all grades) with palbociclib + letrozole vs placebo + letrozole were neutropenia (81.8% vs 6.3%), infections (62.6% vs 45.0%), leukopenia (40.3% vs 2.3%), fatigue (39.6% vs 28.4%), arthralgia (37.6% vs 36.9%), nausea (37.2% vs 27.0%), 14.0%), alopecia (33.6% vs 16.2%), stomatitis (31.5% vs 14.9%). Grade 3/4 neutropenia occurred in 69.1% in patients with palbociclib + letrozole. The incidence rate of neutropenia with combination therapy was higher in the Japanese than in the overall population

(neutropenia, 93.8% vs 79.5%). Grade 3/4 neutropenia occurred in 87.5% of Japanese patients with palbociclib + letrozole. In PALOMA-2, FACT-B was used to assess patient-reported outcome (PRO). There was no significant difference between palbociclib + letrozole and placebo + letrozole in overall change from baseline in FACT-B scores, despite the longer duration of treatment in the combination arm, and no significant difference in FACT-B HRQOL based on FACT-B total scores. The analysis of time to deterioration (TTD) in FACT-B showed a positive trend (hazard ratio<1) favoring the palbociclib + letrozole arm but was not statistically significant (hazard ratio=0.883 [95% CI, 0.673-1.158]; one-sided P=0.19).

Another phase 3 study, PALOMA-3, was conducted with HR+/HER2- patients that had relapsed or progressed during prior endocrine therapy. The median PFS was 9.2 months with palbociclib + fulvestrant and 3.8 months with placebo + fulvestrant (hazard ratio=0.42 [95% CI, 0.32-0.56] P<0.001). In Japanese subgroup analysis in PALOMA-3, median PFS was 13.6 months in palbociclib + fulvestrant and 11.2 months in placebo + fulvestrant group (hazard ratio= 0.82 [95% CI, 0.32-2.11]).

Common AEs with palbociclib + fulvestrant vs placebo + fulvestrant were neutropenia (84.1% vs 3.5%), leukopenia (60.0% vs 5.2%), infections (54.5% vs 34.9%), fatigue (44.1% vs 31.4%), Nausea (35.9% vs 30.8%), Anemia (31.6% vs 14.0%), Stomatitis (30.1% vs 14.0%). Grade 3/4 neutropenia occurred in 69.6% of patients. Among Japanese patients, neutropenia was most common AE in the palbociclib arm (93%) and typically grade 3/4. Accordingly, dose reduction, cycle delays, and dose interruptions were higher in Japanese patients than in the overall populations. In PALOMA-3, EORTC-QLQ-C30 and EORTC-QLQ-BR23 were used to asses PRO. Analysis of PROs between the two treatment groups showed that estimated overall global QOL scores in EORTC-QLQ-C30 significantly favored the palbociclib + fulvestrant (66.1, [95% CI, 64.5-67.7] versus 63.0 [95% CI, 60.6-65.3]; P=0.0313). Significantly greater improvement from baseline in pain was also observed in this group (-3.3 [95% CI, -5.1 to -1.5] versus 2.0, [95% CI -0.6 to 4.6]; p=0.0011]). Also, TTD in global QOL and pain were significantly delayed (hazard ratio=0.64 [95% CI, 0.45-0.91; p<0.007, hazard ratio=0.64 [95% CI, 0.49-0.85; p<0.001, respectively]).

Cancer treatment is taking place in an outpatient setting. The growing number of oral and subcutaneous medications for oncological diseases lead to new challenges for patients and health care providers. Some of the challenges include continuous patient-physician communication, lack of adherence, potential side effects, which are common and often underreported, and their impact on quality of life (QOL). One of the important purposes of treatment for ABC patients is to improve or maintain QOL, thus, appropriate assessment of patients' QOL and the effect to daily life are important and desirable to making appropriate treatment decisions and assisting in timely delivery of care.

ePRO technologies can provide a new opportunity for routine monitoring to assess patients' condition, because the ability to assess PROs in real-time enables quick clinical decision making and intervention. In addition, application of ePRO might enable better patient clinician communication and lower symptom distress. Also, this kind of ministering provides

a systematically collected symptom data and, thus eventually supports clinical decision making to improve symptom management, which could save a lot of health care provider's time, reduce the number of patients' visits and could enhance adherence.

Wearable devices can objectively measure physical activity. With the rapid development and commercialization in recent years, it has become possible to easily measure patients' physical activity using wearable devices. Gresham et al.,2018 summarized 41 randomized trials using wearable devices conducted on cancer patients between 2005 and 2016, consistent with the trend in recent years that increasing number of clinical trials have examined the relationship between physical activity and clinical outcomes. Some of these studies have suggested that the physical activity of cancer patients correlates with the patient's performance status, quality of life and survival.

To date, there have been few studies in Japan evaluating the day-to-day effects of ABC treatment on patients in a real-world setting, and information about the effects of treatment-induced AEs on patients' daily functioning outside the context of clinical trials is particularly lacking. This study will provide prospective, observational data in the real-world setting to evaluate the impact of ABC treatment and the treatment-related AEs on patients' daily life utilizing novel technologies (ie, ePRO and wearable device).

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study A5481126. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Primary objective

Assess change in (1) PRO as measured by EORTC-QLQ-C30 collected via smartphone-based application and (2) physical activity as measured by wearable device in Japanese patients with HR+/HER2- advanced breast cancer receiving below treatment as first or second line setting:

1. *Palbociclib plus endocrine therapy (Group 1) or*
2. *Endocrine monotherapy (Group 2)*

NOTE: The study is not intended to compare outcomes between the two groups as the primary objective.

Secondary objectives

The following research objectives will be addressed separately for both Group 1 and 2.
When associations for group 1 and 2 are similar, the group 1 and 2 will be pooled.

- *Assess the association between change in EORTC-QLQ-C30 and physical activity versus investigator-reported adverse event (AE)*
- *Assess the association between change in EORTC-QLQ-C30 and physical activity versus patient-reported symptom as measured by PRO-CTCAE collected via smartphone-based application*
- *Assess the association between change in EORTC-QLQ-C30 versus change in physical activity*
- *Assess the association between change in EORTC-QLQ-C30 and physical activity versus disease progression*
- *Assess the feasibility of collecting physical activity data with the wearable device in Japanese patients with advanced breast cancer*
- *Assess patient's treatment satisfaction (collected as a single item via smartphone-based application)*
- *Evaluate concordance and discordance between investigator-assessed AE versus PRO-CTCAE*
- *Characterize patients with HR+/HER2- ABC initiating each group treatment (eg, baseline patient demographics and clinical characteristics)*

The following research objectives will be addressed Group 1 only.

- *Describe dosing patterns (eg, dose reduction, dose interruptions, cycle delay)*

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2.2. Study Design

The study is a prospective, multicenter, observational study to evaluate PRO (Health related QOL) and physical activity using smartphone-based application and wearable device in Japanese patients with HR+/HER2- ABC.

Patients will be enrolled into either palbociclib plus endocrine therapy group (Group 1) or endocrine monotherapy group (Group 2) based on the discretion of the treating physician under routine clinical practice. Total target number of patients is approximately one-hundred in this study (About 50 patients in each group).

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Enrolled patients will download a smartphone-based application for electronic PRO (ePRO), be provided access to and trained on the use of the application to complete baseline, daily, weekly, and cycle-based assessments for 6 cycles (24 weeks). In addition, enrolled patients will be provided with wearable device and requested to wear the device at all-times, except of while bathing and sleeping, for 6 cycles (24 weeks).

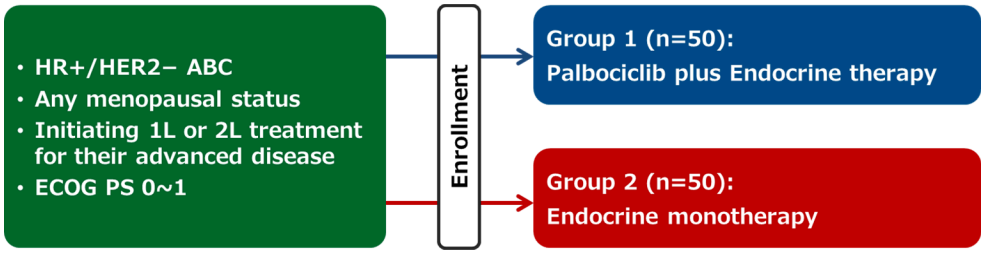
In this study, one cycle is defined as follows;

- *In Group 1 (palbociclib plus endocrine therapy), palbociclib is administered for 3 consecutive weeks followed by 1 week off treatment to comprise one cycle of 4 weeks. If palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of one cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks.*

- *In Group 2 (endocrine monotherapy), one cycle is defined as 4 weeks.*

Participation in this study is not intended to change the routine treatment that patients receive as determined by their prescribing clinicians; all treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician. No additional visits to the clinic will be required for the purposes of the study.

Figure 1. Study Design



It is anticipated that all data collection for this study will occur over a 18-month period (from the first patient's first visit to the last patient's end of study assessment),

Planned patient enrollment duration: 12 months

Planned data collection for an individual patient: 6 cycles (24 weeks)*

**In Group 1, if palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of one cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- *EORTC-QLQ-C30 (Global health status scale)*

  - *The EORTC-QLQ-C30 is a 30-item questionnaire to evaluate cancer patients' QOL, and it's composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.*

  - Change of scores from baseline at each cycle

  - Scores at each cycle

- *Physical activity metrics (Sedentary time)*

  All the physical activity metrics variables will be analyzed with "WEARFILTERED" (ie. "Wear" = TRUE.)

  - Average of a week, which includes 5 or more days of wearing 10 hours or longer during a day except for bedtime.

  - Change from baseline at each week

  - Sedentary time (sedentary time means) at each week

3.2. Secondary Endpoint(s)

- *Other EORTC-QLQ-C30 subscales*

- *Other physical activity metrics (Steps, MVPA time)*

  - The main variables collected and/or derived from wearable device are shown in Table 2.

- *Adverse events and any laboratory abnormalities (Type, incidence, severity, seriousness and relationship to study medications)*

- *PRO-CTCAE (Fatigue and General pain)*
  - *The PRO-CTCAE is a PRO measurement system that includes a library of questions that measure symptomatic adverse events from the patient perspective. Seventy-eight symptom terms that are common in oncology clinical trials can be evaluable with PRO-CTCAE, and each of symptom terms is assessed relative to one or more distinct attributes, including frequency, severity, and/or interference with usual or daily activities. Responses are provided on a five-point Likert scale.*
- *Disease progression*
- *Patient treatment satisfaction*
  - *Treatment satisfaction will be evaluated with single item question (eg, "How satisfied are you with your current breast cancer treatment?"). Responses are provided on a five-point Likert scale.*
- *Palbociclib treatment (including dose, dose reduction, dose interruption, cycle delay)*

Table 2. Physical activity metrics variables from wearable device

Variables	Definition
Steps	Total estimated steps taken per Date.
Wear minutes	*Total minutes of algorithmically detected "wear time"*
Sedentary behavior	Number of total minutes defined as Sedentary Behavior as defined using the Staudenmayer '15 technique.
Light activity	Number of total minutes spent in Light activity category as defined using the Staudenmayer '15 technique.
Moderate activity	*Number of total minutes spent in Moderate activity category as defined using the* Staudenmayer '15 technique.
Vigorous activity	Number of total minutes spent in Vigorous activity category as defined using the Staudenmayer '15 technique.
MVPA	Total estimated number of minutes of Moderate or higher (moderate to vigorous) physical activity per Date as calculated using the Staudenmayer '15 technique.
Calories	Total estimated calories per Date as calculated using the "Hildebrand Nonlinear" technique.
MET	Total estimated METs per Date as calculated using the "Hildebrand Nonlinear" technique.

Note: All the physical activity metrics variables will be analyzed with "WAKEWEARFILTERED" (ie. "Wear" = TRUE. Excludes minutes that fall within a sleep period.)

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3.4. Baseline Variables

Variables	Data Source	Description
Birth Year	eCRF	
Sex	eCRF	1: Male, 2: Female
Ethnicity	eCRF	
Race of Subject	eCRF	
Height	eCRF	Unit: cm
Weight	eCRF	Unit: kg
BMI	eCRF	Automatically calculated by the following formula BMI = weight (kg)/Height $(m)^2$
Medical History Term	eCRF	MedDRA terms including Lowest Level Term, Preferred Term, High Level Term, High Level Group Term, Primary System Organ Class) will be provided by auto-encoding
Name of Medication (Prior Drug Treatment for Breast Cancer)	eCRF	Standardized Medication Name based on WHO-DRUG will be provided by auto-encoding.
Reason for Stopping Therapy (Prior Drug Treatment for Breast Cancer)	eCRF	
Treatment (Prior Surgery for Breast Cancer)	eCRF	MedDRA terms including Lowest Level Term, Preferred Term, High Level Term, High Level Group Term, Primary System Organ Class) will be provided by auto-encoding
Date of initial diagnosis (Primary Diagnosis)	eCRF	
Date Recurrence/Metastatic (Primary Diagnosis)	eCRF	

Variables	Data Source	Description
TNM Stage Initial Diagnosis (Primary Diagnosis)	eCRF	
Metastatic Site (Primary Diagnosis)	eCRF	
Menopausal status	eCRF	
ECOG Performance Status	eCRF	
Line or therapy	eCRF	
Education	ePRO	
Employment	ePRO	
Physical activity	ActiGraph	Metrics for analysis are undergoing consideration.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the informed consent document.
Evaluable	All participants who enrolled in the study and who respond at least 1 item or measured at least 1 metrics of study application or device. Participants will be analyzed according to the enrolled group.
Safety	All participants who receive at least 1 dose of palbociclib or endocrine therapy. Participants will be analyzed according to the enrolled group. An enrolled but not treated participant will be excluded from the safety analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

Primary analysis will be performed when 100% primary endpoint data will be available.

5.1. Hypotheses and Decision Rules

The study objective is description. We don’t plan to make decision about efficacy and safety of the drugs based on statistical test.

5.2. General Methods

All endpoints will be summarized by descriptive statistics.

As a secondary analysis, we will perform t-test or nonparametric test (if needed) to assess the association between primary endpoints and adverse events and disease progression. CCI [redacted]

5.3. Methods to Manage Missing Data

In the primary analysis, missing data will be excluded from the analysis at each measured point. For calculating scores of EORTC-QLQ-C30 and PRO-CTCAE, missing data will be handled according to the guidance of the developers.

6. ANALYSES AND SUMMARIES

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted.

All variables will be summarized descriptively through tabular displays of the number of observations, mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables by measured points.

6.1. Primary Endpoint(s)

6.1.1. Change in "EORTC-QLQ-C30 (Global health status scale)"

6.1.1.1. Main Analysis

As primary analysis of EORTC-QLQ-C30, change in "Global health status scale" from baseline is summarized at each measurement time point, separately by groups. Baseline values are those measured between enrollment and the day before treatment start.

For patients who could not be measured before treatment start, the values measured within 6 days of the treatment start is treated as the baseline value.

Least squared mean and the 95% CI of the score for each cycle will be estimated using mixed effect model for repeated measures. The covariates included in the model will be group, cycle (categorical variable), group -and-cycle interaction term, and baseline score.

6.1.1.2. Secondary analysis

The same analysis for the raw value of "EORTC-QLQ-C30 (Global health status scale)" is performed as for change in "EORTC-QLQ-C30 (Global health status)" (6.1.1.1.).

6.1.2. Change in "Sedentary time" (Sedentary time means)

6.1.2.1. Main Analysis

Physical activity metrics are averaged at weekly basis. As primary analysis of physical activity, change in "Sedentary time" from baseline is summarized at weekly basis, separately by groups. Baseline values are the average number of those measured between enrollment and the day before treatment start (the baseline observation period).

For patients with less than 4 days of measurements before the treatment start, the measurements from the first 4 days are used.

Least squared mean and the 95% CI of the score for each cycle will be estimated using mixed effect model for repeated measures. The covariates included in the model will be group, cycle (categorical variable), group -and-cycle interaction term, week of each cycle, and baseline score.

The same analysis will be performed for the population excluding patients who had less than 4 days of measurements prior to the start of treatment.

6.1.2.2. Secondary Analysis

- ✓ The same analysis for the raw value of "Sedentary time (Sedentary time means)" are performed as for change in "Sedentary time (Sedentary time means)" (6.1.2.1).

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6.2. Secondary Endpoint(s)

6.2.1. EORTC-QLQ-C30 scores

- ✓ The same analysis for other 14 scales of EORTC-QLQ-C30 (5 functional scales [physical, role, emotional, cognitive, and social functioning], 8 symptom scales [fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea], and financial difficulties scale) are performed as for global health status.

- ✓ Following analyses of 5 functional scales and Global health status scale of EORTC-QLQ-C30 are performed to assess the associations as follows:

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When associations for group 1 and 2 were similar, the group 1 and 2 will be pooled.

- Tabulate patients with and without selected investigator-reported AE at each cycle, summarize the mean values of change in EORTC-QLQ-C30 from baseline at each cycle in each tabulated population, and compare the results at Cycle 1 and Cycle 3 using t-test

- Tabulate patients with and without symptom of PRO-CTCAE at each cycle, summarize the mean values of change in EORTC-QLQ-C30 from baseline at each cycle in each tabulated population, and compare the results at Cycle 1 and Cycle 3 using t-test

- Tabulate patients with disease progression during the observation period, and summarize the mean values of EORTC-QLQ-C30 before and after disease progression

6.2.2. Physical activity metrics

✓ The same analysis for other physical activity metrics (steps, MVPA time) is performed as for Sedentary time.

✓ The similar analyses of each physical activity metrics, as same as that for EORTC-QLQ-C30, are performed to assess the associations.

6.2.3. Association between EORTC-QLQ-C30 and Physical activity

✓ The Pearson's correlations between change in PRO and physical activity metrics will be calculated at each measurement time point.

6.2.4. Patient satisfaction

✓ Patient satisfaction will be summarized descriptively through tabular displays of frequency distributions of categorical variables, by measured points.

6.2.5. Adverse events and PRO-CTCAE

✓ Investigator-reported AE and patient-reported AE will be summarized.

✓ Association between investigator-reported AE and patient-reported AE will be assessed using contingency table and weighted Kappa coefficient.

6.2.6. Feasibility of the measures

✓ The number of responses from EORTC-QLQ-C30 and the number of physical activity data are summarized at each measurement point.

✓ Time from enrollment to discontinue wearing the device (ie, Time-to-wearable failure) is calculated, and the cumulative rate curve, median, and proportion of time-point continuation are estimated using the Kaplan-Meier method.

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6.4. Subset Analyses

✓ Prespecified subset variables for analyses of primary endpoints as follows;

- Age(59 years of age or younger/ 60 years of age or older),
- menopausal status (premenopausal/ postmenopausal),
- PS(0/ 1),
- line of therapy (first/ second),
- employment (none or retired/ fulltime or parttime)
- Education(~ high school diploma or equialent/ College ~)
- Visceral metastatic (presence/ absence)
- Stage (I-III/ IV), (I-II/ III-IV),
- BMI(18.5 kg/m2 or lower / higher than 18.5 kg/m2)
- Experience of dose reduction (presence/ absence)
- Experience of fatigue (presence/ absence)Pre-dore reduction/ post-dose reduction (among patients with dose reductions)

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline characteristics presented in Section 3.4 will be summarized using descriptive statistics.

6.5.2. Study Conduct and Participant Disposition

An accounting of the study patients will be tabulated including enrolled, evaluable for PRO, and safety (treated). Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation.

Reasons for premature discontinuation will be summarized. Unexpected treatment (e.g., palbociclib therapy in Group 2) will be described.

6.5.3. Study Treatment Exposure

The extent of treatment will be summarized as follows:

- Number of cycles started
- Duration of a cycle (weeks)

For Group 1 (palbociclib plus endocrine therapy)

- Starting dose: 125 mg, 100 mg, 75 mg
- Number of patients with no dose reduction, at least 1 dose reduction, 2 dose reductions
- Patients with cycle delay

6.5.4. Concomitant Medications and Nondrug Treatments

Radiation treatment and general surgery during the observation period and follow-up cancer therapy will be listed and summarized.

6.6. Safety Summaries and Analyses

Overall safety profile as characterized by type, frequency, severity of adverse events as graded by NCI Common Toxicity Criteria for Adverse Events version 4 (NCI CTCAE v.4.0), timing and relationship to treatment.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4. For other AEs without specific CTCAE definitions, results are identified according to CTCAE “other” categories.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v.4.0 Grade 3 or higher, treatment-related events, study procedure-related events and serious adverse events will be considered with special attention.

Patients who start treatment are assessed for toxicities up to 28 days after the final dose of treatment or start of new treatment (whichever comes first). Toxicities observed beyond 28 days and recorded in the database per Sponsor’s agreement will be included in the summaries.

Frequency distributions of the worst grade of the adverse events will be summarized for all-causality and treatment-related adverse events, respectively. Grade 3 or higher events, serious adverse events, discontinuations due to adverse events will be summarized separately for all-causality and treatment-related adverse events. All adverse events including deaths and serious adverse events will be listed.

7. INTERIM ANALYSES

Not applicable (No interim analysis is planned during study period)

8. REFERENCES

Not Applicable

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Not Applicable

Appendix 2. List of Abbreviations

Abbreviation	Term
1L	First-Line
2L	Second-Line
95% CI	95% Confidence Interval
ABC	Advanced Breast Cancer
AE(s)	Adverse Event(s)
BMI	Body Mass Index
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CTCAE	Common Terminology Criteria for Adverse Events
CM	Centimeter
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC-QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast23
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients30
ePRO	electronic Patient-Reported Outcome
ER	Estrogen Receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast
HER2	Human Epidermal Growth Factor Receptor-2
HR	Hormone Receptor
HRQOL	Health Related Quality of Life
KG	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MVPA	Moderate-to-Vigorous Physical Activity
NCI	National Cancer Institute
PFS	Progression-Free Survival
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcome - Common Terminology Criteria for Adverse Events
QOL	Quality of Life
SAP	Statistical Analysis Plan

Abbreviation	Term
TTD	Time to Deterioration
WHO	World Health Organization