NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**POLARIS**: Palbociclib in Hormone Receptor Positive Advanced Breast Cancer: A Prospective Multicenter Non-Interventional Study
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Research question and objectives	This Non-Interventional Study will describe and analyze the clinical use of palbociclib in routine clinical practice in the treatment of advanced breast cancer. Main objectives: • Palbociclib prescribing and treatment patterns in routine clinical practice in Advanced Breast Cancer (ABC) treatment • Clinical outcomes • Metastatic Breast Cancer (MBC) treatment sequence • Patient quality of life • Geriatric assessments CCI [redacted]
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced breast cancer
AE	Adverse event
AEM	Adverse event monitoring
ADL	Activities of Daily Living
CAN	Canada
CBC	Complete blood count
CDK	Cyclin Dependent Kinase
cfDNA	Circulating cell free deoxyribonucleic acid
CGA	Comprehensive Geriatric Assessment
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
eCRF	Electronic case report form
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EDP	Exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ER	Estrogen receptor
ER+	Estrogen receptor positive
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GA	Geriatric Assessment
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HER2-	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HR+	Hormone receptor positive
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional review board
ISMF	Investigator Site Master File
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MBC	Metastatic breast cancer
NCCN	National Comprehensive Cancer Network
NIS	Non-interventional study
PFS	Progression free survival
PR+	Progesterone receptor positive

PRO	Patient reported outcomes
PV	Pharmacovigilance
QOL	Quality of life
RB	Retinoblastoma
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SIOG	Society of Geriatric Oncology
SOC	Standard of care
SOP	Standard operating procedure
US	United States

2. RESPONSIBLE PARTIES

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3. ABSTRACT

POLARIS: Palbociclib in Hormone Receptor Positive Advanced Breast Cancer: A Prospective Multicenter Non-Interventional Study (NIS)

BACKGROUND: Palbociclib is a novel cyclin dependent kinase (CDK)4/6 inhibitor approved in the United States (US) and Canada (CAN) in combination with certain endocrine therapies for hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC). With the introduction of this first in class therapy, it is important to understand palbociclib treatment patterns in routine clinical practice in the US and CAN; and as a result, the evolving treatment landscape of ABC. This study will provide prospective, observational data in the real world setting to contribute to the knowledge of palbociclib in ABC disease management and the new ABC treatment paradigm.

OBJECTIVES: The objectives of this prospective NIS of palbociclib in ABC treatment are to describe and analyze palbociclib prescribing and treatment patterns in routine clinical practice, clinical outcomes, metastatic breast cancer (MBC) treatment sequencing prior to, during, and after palbociclib, patient quality of life, geriatric specific assessment; and CCI [redacted]

STUDY DESIGN: A prospective, observational, NIS.

POPULATION: HR+/HER2- ABC patients whose treatment decision with palbociclib has been made by their treating physician and who meet the eligibility criteria will be invited to participate in the study.

DATA SOURCES: This prospective, observational study will be conducted according to each site's routine clinical practice. Data will be captured using a web-based collection tool.

STUDY SIZE: Approximately 1500 patients from approximately 100 US sites and 10 CAN sites (community and academic) will be enrolled. Study duration will consist of observation of patients on palbociclib treatment and approximately 3 years of follow-up post each patient's end of treatment with palbociclib, or until patient withdrawal from the study or death.

DATA ANALYSIS: Descriptive statistics will be used to summarize all endpoints.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	02AUG 2017	Substantial	Study Information Section 1. List of Abbreviations Section 3. Abstract Section 6. Background and Rationale Section 7. Research Objectives and Questions Section 8. Research Methods Section 12. References	Study Information: Research objectives and questions updated to include clinical outcomes as a main objective. Section 1. List of Abbreviations: Canada added to the table. Section 3. Abstract: Updated to include approximately 10 Canadian sites, and added clinical outcomes as a main objective. Section 6. Background and Rationale: Updated to include Canada and provide background information on Canadian Breast Cancer Statistics. Section 7. Research Objective and Question: Main research objectives updated to include clinical outcomes. Section 8. Research Methods: Updated to include approximately 10 sites in Canada. Section 8. Table 1: Data Entry Schedule: Footnotes updated to clarify physician MBC treatment selection survey, CCI [redacted] clarify CBC data collection, and clarify reporting of adverse event data. CCI [redacted] [redacted] Section 12. References: References updated.	Study amended to include Canada for participation, specify clinical outcomes as a research main objective, and update the data entry table to clarify safety reporting time period, CCI [redacted] potential analysis and clarify CBC data entry and references were updated.

5. MILESTONES

Milestone	Planned date
Start of data collection	16Dec2016
End of data collection	16Dec2021
Final study report	15NOV2022

6. RATIONALE AND BACKGROUND

6.1. Breast Cancer

Breast cancer remains the most common cancer in women worldwide, with 1.6 million new cases diagnosed and a half a million deaths reported annually. In the US, an estimated 246,660 new cases of invasive breast cancer, and an additional 61,000 new cases of in situ breast cancer, are expected to be diagnosed in 2016 (American Cancer Society, 2016). Breast cancer is ranked the second highest cause of cancer death in American women (American Cancer Society, 2016) and is the third highest cause of cancer death overall, behind lung cancer and colon/rectum cancer, with 40,450 estimated deaths in the US in 2016 (Howlader et al 2016). Breast cancer represents about 29% of all new cancer cases and 14% of all cancer deaths in women in the US (American Cancer Society, 2016). From 2003 to 2012, breast cancer incidence rates in the US were stable in white women and increased slightly, at rate of 0.3% per year, in black women. While death rates declined over the same time period (by 1.9% in white women and 1.4% in black women), due to early detection and treatment (American Cancer Society, 2016), breast cancer still remains a major heath issue in the US. Statistics for breast cancer in males are also notable: 2,600 new cases are expected to be diagnosed in the US in 2016, with 440 estimated deaths (American Cancer Society, 2016).

According to latest figures from the Canadian Cancer Society (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016), 1 in 9 Canadian women are expected to develop breast cancer in their lifetime, with 25,700 expected new cases in 2016. Breast cancer is the second most common cause of cancer death in Canadian women, accounting for 13% of all cancer deaths in women, and is the third most common cancer in Canada (CAN), accounting for 13% of all cancers and 26% of cancers among women. Consistent with data from the US, breast cancer incidence rate in CAN stabilized from 2004 through 2010 and the death rate due to breast cancer has fallen from a peak of 41.7 deaths per 100,000 in 1987 to a projected rate of 23.4 deaths per 100,000 in 2016 (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2016).

Approximately 80% of breast cancers expressed estrogen receptor (ER), progesterone receptor (PR), or both. Endocrine therapy is the mainstream treatment for the HR+ cancers. Currently, first-line treatment in the ER+/HER2-ABC postmenopausal population typically includes endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen with time to progression and prolongation of progression free survival (PFS) ranging from 5 to 15 months (Cardoso, 2012; Bergh, 2012; Mehta, 2012). These treatment options are supported by clinical practice guidelines published by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) as preferred first-line options in patients who are antiestrogen naïve or who are more than 2 years from previous antiestrogen therapy and do not have extensive visceral involvement (Cardoso, 2012; NCCN, 2016). Single-agent treatment with an aromatase inhibitor or tamoxifen has shown limited clinical benefit (Baselga et al 2012; Klijn et al 2000). The selective ER degrader fulvestrant has modest activity in this population of patients (Di Leo et al 2010, 2014) and the development of effective therapies that can address resistance to endocrine therapy is of clinical importance.

6.2. Palbociclib

In vitro evidence suggests that breast cancer that has developed resistance to prior endocrine therapy remains dependent on cyclin D1–CDK4/6 to promote proliferation (Miller et al, 2011; Thangavel et al, 2011). Palbociclib is an orally bioavailable small-molecule inhibitor of CDK4 and CDK6, with a high level of selectivity for CDK4 and CDK6 over other cyclin-dependent kinases (Toogood et al, 2005). Palbociclib inhibits CDK4 and CDK6 in vitro, resulting in loss of retinoblastoma (RB)1 phosphorylation. It has high activity in hormone-receptor–positive breast-cancer cell lines and is synergistic in combination with endocrine therapies (Finn et al, 2009).

In a phase 1/2 study, PALOMA-1 (Finn et al, 2015), patients were randomized to a 1:1 ratio to receive palbociclib + letrozole or letrozole alone. The median PFS was 20.2 months with palbociclib + letrozole and 10.2 months with letrozole alone (Hazard ratio [HR]=0.488; *P*=0.0004). In terms of the safety profile, Grade 3/4 neutropenia was significantly higher in patients receiving palbociclib + letrozole compared with letrozole alone (54% vs 1%). Additionally, the rate of Grade 3/4 leucopenia (19% vs 0%) and fatigue (4% vs 1%) were also higher with palbociclib + letrozole. No cases of febrile neutropenia or neutropenia-related infections were reported in the study (Finn et al, 2015).

A phase 3 study, PALOMA-2 (Finn et al, 2016), was conducted with 666 post-menopausal women without prior systemic therapy for ER+/HER2– ABC. Patients were randomized to a 2:1 ratio to receive palbociclib + letrozole or placebo + letrozole. The median PFS was 24.8 months with palbociclib + letrozole and 14.5 months with placebo + letrozole (HR=0.58; 95% confidence interval [CI] 0.46, 0.72, *P*<0.000001). Common adverse events (AEs; all grades) with palbociclib + letrozole vs placebo + letrozole were neutropenia (75% vs 5%), fatigue (41% vs 23%), nausea (25% vs 13%), arthralgia (33.3% vs 33.8%), and alopecia (32.9% vs 15.8%). Grade 3/4 neutropenia occurred in54% of patients; other AEs were of Grade 1 severity. Febrile neutropenia was seen only with palbociclib + letrozole (2.5%). Permanent discontinuation due to AEs occurred in 9.7% of patients receiving palbociclib + letrozole vs 5.9% receiving placebo + letrozole. PALOMA-2 confirmed the significant clinical benefit and safety of palbociclib + letrozole in ER+/HER2– ABC patients who had not received prior systemic therapy for their advanced disease (Finn et al, 2016).

Another phase 3 study, PALOMA-3, was conducted with 521 patients with advanced HR+/HER2– patients that had relapsed or progressed during prior endocrine therapy (Turner et al, 2015). Patients were randomized to a 2:1 ratio to receive palbociclib + fulvestrant or placebo + fulvestrant. The median PFS was 9.2 months (95% CI, 7.5, upper limit not estimable) with palbociclib + fulvestrant and 3.8 months (95% CI 3.5, 5.5) with placebo + fulvestrant (HR for disease progression or death, 0.42; 95% CI 0.32, 0.56; P<0.001). The most common grade 3 or 4 AEs in the palbociclib+fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo + fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of patients in each treatment group. The rate of discontinuation due to AEs was 2.6% vs. 1.7% (Turner et al, 2015).

Estrogen receptor-positive breast cancer is biologically heterogeneous. Although palbociclib clinical trial results are very promising, it is also recognized that not all patients may respond to palbociclib treatment, and palbociclib treatment does come with mechanism based toxicities. CCI [redacted]

6.3. EORTC QLQ-C30

In recent years, progress has been made in using patient-reported outcome (PRO) measures to determine how patients experience their disease over the course of treatment, receive aftercare, and live with cancer as a chronic condition. There is a growing demand for routine monitoring of PROs to complement clinical data with the patient's perspective (Wintner et al, 2016) and to evaluate cancer treatment-related symptoms, which are common and often underreported (American Cancer Society 2016).

The European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (Luckett et al 2011; Velikova et al, 2012; Wintner et al, 2016) is widely used to assess changes in quality of life for patients undergoing treatment for cancer. The EORTC QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, cognitive emotional, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global health/quality of life (QOL) subscale, and six single items assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and the financial impact of cancer), with responses based on recall during the past week (see Annex 1: Stand Alone Documents: EORTC QLQ-C30). The EORTC QLQ-C30 has been translated and linguistically validated into more than 60 languages (Velikova et al, 2012).

6.4. Geriatric Assessments

The median age at diagnosis of breast cancer in the US is 62 years, and the majority of women who die of breast cancer in the US are age 65 years and older (median: 68 years) (Howlader et al 2016). In CAN, the majority (51%) of breast cancers occur in women 50 to 69 years of age, and approximately 32% of breast cancers are diagnosed in females aged 70 and over (Canadian Cancer Society, 2016). The US population that is 80 years and older is rapidly expanding—from 9 million members in 2001 to an anticipated 30 million members by 2050 (United Nations, 2001; Shachar et al, 2016a,b). As a group, older adults are more vulnerable to the adverse effects of cancer when compared with younger patients, in large part because of their higher incidence of comorbidities, their frequent use of many concomitant medications, and age-associated physiologic changes that may affect organ function (Schachar et al 2016b). To understand the population better in order to provide more appropriate treatment options, in 2005 the International Society of Geriatric Oncology (SIOG) recommended the use of geriatric assessment in cancer patients aged 70 years or older (Decoster et al, 2015). It is believed that the plausible data from the geriatric assessment can help devise treatment strategy and maximize the benefit of treatment outcome. Based on the lack of information in this population (Schachar et al 2016a,b), it is intended that the geriatric assessment effectively addresses these and many other areas of

geriatric care that are crucial to the successful treatment and prevention of disease and disability in older people, especially in cancer patients.

The comprehensive geriatric assessment (CGA) is a multidimensional, multidisciplinary assessment designed to evaluate an older person's functional ability, physical health, cognition and mental health, and socioenvironmental circumstances (Elsawy and Higgins, 2011). CGA has been found to improve treatment outcomes in older patients in the areas of prediction of treatment related toxicities, treatment adherence, quality of life, treatment decision making, and overall survival (Owusu and Berger 2014). A lack of consensus remains as to which domains to be included in a CGA, and what subsequent assessment and interventions to be used. CGA is time consuming and makes implementation in busy clinical practice challenging (Hurria et al, 2005).

Several screening tools have been developed as brief assessment in older patients, to identify vulnerable patients in need of full CGA. These tools may also have prognostic or predictive value in the outcome measures of treatment related toxicity, functional decline and survival (Decoster et al, 2015). One of the most studied screening tools for elderly cancer patients is G8 Screening Tool, which will be completed in the current protocol only for patients equal to or greater than 70 years of age at the time of study enrollment. The G8 was introduced by Bellera et al. in 2012 as a physician-assessed tool to identify geriatric cancer patients for whom the administration of a time consuming comprehensive geriatric assessment would be beneficial. Patients can fill in this instrument with the assistance of a healthcare professional (Soubeyran et al, 2014). The G8 has shown high sensitivity and specificity among different screening tools (Decoster et al, 2015; Hentschel et al, 2016; Martinez-Tapia et al, 2016). Eight items are included, based mainly on nutritional status, with responses based on recall for up to 3 months. The G8 has been found predictive for chemotherapy-related toxicity (Stokoe et al, 2012.) and prognostic for survival in mostly solid tumors (Liuu et al, 2012; Kenis et al 2014). A score of less than or equal to 14 indicates further full assessment may be needed (Bellera et al, 2012).

An additional screening tool that will be completed only for patients equal to or greater than 70 years of age at the time of study enrollment is activities of daily living (ADL). Although not specifically designed for geriatric patients, ADL assesses basic self-care skills to maintain independence in home (bathing, dressing toileting, feeding oneself, maintain continent, transferring from bed/chair). Studies have shown that functional status predicts survival, chemotherapy toxicity, postoperative morbidity, mortality (Eberhadt et al, 2006; Maione et al, 2005). Correlation of ADL dependence and outcome is less established in studies of older patients receiving outpatient oncology care, likely because there is a low proportion of patients requiring this degree of assistance (Extermann and Hurria, 2007.

Elderly patients have not been significantly represented in clinical trials for targeted therapies for breast cancer, including those that led to registration of palbociclib (Shachar et al, 2016). Additional research on older patients being treated with palbociclib, such as in routine clinical practice setting, may generate data to bridge the gap in understanding the tolerability and outcomes in this venerable patient population, commonly with comorbidities and declining general health due to aging.

6.5. Summary

Palbociclib is a novel CDK4/6 inhibitor approved in US and CAN in combination with certain endocrine therapies for HR+/HER2- ABC. With the introduction of this first in a new class of drugs, it is important to understand palbociclib treatment patterns in routine clinical practice in the US and CAN and, as a result, the evolving treatment landscape of ABC. It is important to understand real-world practice patterns and patient reported outcomes as clinical trial populations may not be representative of the target populations of patients given the enrollment criteria in clinical trials coupled with the focus on a single line of therapy. This study will provide prospective, observational data in the real world setting to contribute to the knowledge of palbociclib in ABC disease management and the new ABC treatment paradigm, and CCI [redacted] It is also of value to understand patient quality of life and the utility of geriatric assessment (GA) screening tools in treatment outcome measures of older breast cancer patients to further inform treatment decisions.

7. RESEARCH QUESTIONS AND OBJECTIVES

The objectives of this prospective NIS of palbociclib in ABC treatment are to describe and analyze palbociclib prescribing and treatment patterns in routine clinical practice, clinical outcomes, MBC treatment sequencing prior to, during, and after palbociclib, patient quality of life, geriatric specific assessment; and CCI [redacted]

The main research questions to be addressed may include the following:

- Palbociclib prescribing and treatment patterns in routine clinical practice in ABC treatment
- Clinical outcomes
- MBC treatment sequence
- Patient quality of life, as measured by EORTC QLQ-C30
- Geriatric Assessments in patients equal to or greater than 70 years of age at enrollment

CCI [redacted]

[redacted]

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, non-interventional (NI), multicenter study being conducted in the US and CAN. The primary goal is to understand palbociclib prescribing and treatment patterns for patients with ABC being treated in routine clinical practice in the US and CAN.

Approximately 1,500 subjects will be enrolled across approximately 100 sites in the US and 10 sites in CAN. Study duration will consist of observation of patients on palbociclib treatment and approximately 3 years of follow-up post each patient's end of treatment with palbociclib, or until patient withdrawal from the study or death.

Participation in this study is not intended to change the routine treatment patients receive, as determined by their prescribing physicians; all treatment decisions, type and timing of disease monitoring are at the discretion of treating physician and patient.

Assessments include patient questionnaires and quality of life (EORTC QLQ-C30, G8 Screening Tool, ADL), site questionnaires, physician MBC treatment selection survey, and CCI [redacted], as detailed in Section 8.3 and Section 8.4.

8.2. Setting

Patients with HR+/HER2- ABC within the US and CAN will be enrolled from a geographically representative population as well as from diverse treatment settings (e.g., academic and community sites). ABC patients whose treatment decision with palbociclib has been made by their treating physician and meet the eligibility criteria will be invited to participate in the study. Eligibility will be assessed at the date of the enrollment visit (i.e. Baseline/Visit 1).

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Age ≥18 years or older.
2. Diagnosis of adenocarcinoma of the breast with evidence of metastatic disease or advanced disease not amenable to treatment with curative intent.
3. Documented HR+ (ER+ and/or PR+) tumor based on local standards.
4. Documented HER2- tumor based on local standards.
5. Physician has determined that treatment with palbociclib is indicated.
6. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

7. Patients who in the opinion of the investigator are willing and able to comply with regular clinic visits as per standard of care practice at the site.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with a life expectancy of less than 3 months at the time of ABC diagnosis, per the investigator's judgment.

2. Patients participating in any interventional clinical trial that includes investigational or marketed products at the time of enrollment. (Patients participating in other investigator initiated research or NIS can be included as long as their standard of care is not altered by the study).

3. Patients on active treatment for malignancies other than ABC at the time of enrollment.

4. Patients who are unable to understand the nature of the study and are unwilling to sign an informed consent.

Patient eligibility should be reviewed, documented, and confirmed by an appropriately qualified member of the investigator's study team before patients are enrolled in the study.

8.3. Variables

Patient demographics, study site characteristics, medical history, baseline concomitant medications, breast cancer diagnosis and recurrence history, metastatic disease status, MBC treatment, disease status and characteristics, performance status (ECOG), palbociclib dosing and treatment management, routine clinical efficacy assessment, physician MBC treatment selection survey, quality of life, geriatric screening tool and questionnaire, and CCI will be assessed. Detailed definitions of variables that will be collected or derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP).

Data collected will be from the treating physicians' routine clinical assessments as per their local standard of care. Patients will be asked to complete the EORTC QLQ-C30; the G8 Geriatric Screening Tool and ADL will be completed for patients greater than or equal to 70 years of age at the time of study enrollment. The G8 Screening Tool will be completed by the treating physician or appropriately delegated site staff and the ADL will be completed by the patient or in conjunction with the appropriately delegated site staff. CCI

The Data Entry Schedule is provided in Table 1 and the EORTC QLQ-C30 and Geriatric Assessments in Table 2.

Table 1: Data Entry Schedule

Data Collection and Entry[1] ►	Baseline	During Treatment with Palbociclib	Post Treatment with Palbociclib
	SOC Visit 1	SOC Visit 2 through End of Treatment with Palbociclib	Follow-up through End of Study[2]
Informed Consent & Inclusion/Exclusion Criteria	x		
Patient Demographics, Study Site Characteristics, Medical History, Baseline Concomitant Medications, Baseline Metastatic Disease Status	x		
Breast Cancer Diagnosis and Recurrence History	x		
Breast Cancer Treatment[3]	x[3]	x[3]	x[3]
Physician MBC Treatment Selection Survey[4]	x[4]	x[4]	x[4]
Performance Status (ECOG)	x	x	
Clinical Assessments[5]	x[5]	x[5]	x[5]
[redacted] CCI	[redacted]	[redacted]	
Laboratory: CBC[7]	x[7]	x[7]	
Adverse Events and Serious Adverse Events[8]	x[8]	x[8]	

SOC = Standard of care; ABC = advanced breast cancer; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; MBC = metastatic breast cancer; SAE = serious adverse event

1. Data is collected in accordance with normal standard of care visits, enter all data available per Data Entry Schedule into the electronic data capture system.
2. Follow up through End of Study: Enter data at SOC visits where each subsequent (post palbociclib treatment) MBC treatment regimen is prescribed and at end of study.
3. Breast cancer treatment: including surgery, radiation, systemic chemotherapy, hormone therapy, and/or targeted therapy, in both neoadjuvant/adjuvant and metastatic disease settings, prior to, during, and post palbociclib treatment; supportive care is also collected in the metastatic setting while on this study.
4. Physician MBC Treatment Selection Survey: Treating physicians will complete a treating physician MBC treatment selection survey that will capture the reason(s) for treatment choice at start of palbociclib therapy and at start of subsequent therapies.
5. Clinical assessments: overall clinical response as judged by treating physician, at intervals per standard of care schedule: imaging assessment, clinical progression, and clinical biomarkers.

CCI [redacted]

7. CBC: Baseline and during palbociclib treatment, enter any CBC during the 1st 3 cycles, then enter Day 1 (or prior to start of a new cycle) CBC for the subsequent cycles as per standard of care.
8. AE/SAE reporting begins at the time of the patient's first dose of palbociclib or the time of the patient's informed consent if s/he is already exposed to palbociclib and up to 28 calendar days following the last administration of palbociclib.

Table 2: EORTC QLQ-C30 and Geriatric Assessments

Data Collection and Entry	Baseline	
►	SOC Visit 1	Through End of Treatment with Palbociclib
EORTC QLQ-C30[1]	x[1]	x[1]
G8 Screening Tool[2]	x[2]	x[2]
ADL: Activities of Daily Living[2]	x[2]	x[2]

ADL = Activities of Daily Living; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30

1. EORTC QLQ-C30 will be collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib.
2. G8 Screening Tool and Activities of Daily Living to be completed only for patients equal to or greater than 70 years of age at the time of study enrollment. G8 and ADL will be collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib. ADL to be completed by the patient or in conjunction with the appropriately delegated site staff, G8 to be completed by the treating physician or the appropriately delegated site staff.

8.4. Data Sources

All data collected in this study are intended to capture the real world treatment patterns and outcomes of patients with HR+, HER2- ABC. An electronic case report form (eCRF) will be used for data collection. The eCRF must be signed by the investigator. The signature serves to attest that the information contained on the eCRF is true. At all times, the investigator has the final responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the eCRFs.

Data for this study will be obtained via the sources outlined below.

8.4.1. Patient Medical Charts

The investigator or authorized medical staff will record clinical and treatment data from patients' existing medical records into an eCRF following each patient's standard of care clinic visit.

8.4.2. Patient Questionnaires and Quality of Life

All patients enrolled in the study will be asked to participate in completing the Quality of Life instrument and Questionnaires:

- EORTC QLQ-C30 (see Annex 1 Stand Alone Documents: EORTC QLQ-C30): Collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib.

- G8 Screening Tool (see Annex 1 Stand Alone Documents: G8 Geriatric Screening Tool) and ADL (see Annex 1 Stand Alone Documents: ADL Activities of Daily Living): Collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib. ADL to be completed by the patient or in conjunction with the appropriately delegated site staff, G8 to be completed by the treating physician or the appropriately delegated site staff.

Patients can complete these assessments either on a paper form or via an electronic direct patient data capture software system.

8.4.3. Site Questionnaires

The following site questionnaires will be completed:

- Study Site Characteristics: A study site information form will be used to collect information at baseline pertaining to the practice, patient population, specialty and treatment pathways.

- Physician MBC Treatment Selection Survey: Treating physicians will also be asked to complete a treating physician MBC treatment selection survey that will capture the

reason(s) for treatment choice at start of palbociclib therapy and at start of subsequent therapies.

CCI [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

8.5. Study Size

This is an observational study of drug usage without any pre-defined hypothesis to be tested; rather, it addresses descriptive objectives. The estimated sample size is applied to ensure adequate exploration of the objectives and sufficient generalizability.

Power Analysis and Sample Size (PASS 13) Software (NCSS Statistical Software, 2014) was used to calculate sample size. Sample sizes are based on a range of conservative estimates for univariate statistics (hypothesis test and confidence intervals) for both dichotomous and continuous outcomes.

Dichotomous Outcomes

Hypothesis testing: A sample size of 1287 achieves 90% power to detect a difference (P_1-P_0) of 0.04 using a two-sided Z test. The target significance level is 0.05. These results assume that the population proportion under the null hypothesis is 0.243 (Zar 1984; Lachin 2000; Fleiss et al, 2003; Chow 2011; Machin et al, 2011; DeSantis et al, 2014). If the null proportion is 0.163 (Tevaarwerk et al, 2013) this sample size has >90% power (Table 3).

Table 3: Sample Size for Proportion Hypothesis Test at α=0.05

P_1-P_0	P_0	Power	N
.04	0.163	0.80	753
.04	0.163	0.85	856
.04	0.163	0.90	1004
.05	0.163	0.80	489
.05	0.163	0.85	567
.05	0.163	0.90	657
.04	0.243	0.80	955
.04	0.243	0.85	1009
.04	0.243	0.90	1287
.05	0.243	0.80	625
.05	0.243	0.85	714
.05	0.243	0.90	834

P_0 is the value of the population proportion under the null hypothesis.
P_1 is the value of the population proportion under the alternative hypothesis.

Confidence Interval: When the sample size is 1134, a two-sided 95% CI for a single proportion using the large sample normal approximation will extend 0.025 (=0.05/2) from the observed proportion for an expected proportion of 0.243(Newcombe 1998; Fleiss et al, 2003; DeSantis et al, 2014). Similarly, when the sample size is 1134, a two-sided 95% CI for a single proportion using the large sample normal approximation will extend 0.029 (=0.058/2) from the observed proportion for an expected proportion of 0.50. This sample is adequate if the null proportion is 0.163 (Tevaarwerk et al, 2013) (Table 4).

Table 4: Sample Size 95% Confidence Interval for a Proportion at α=0.05

CI Width	Proportion (p)	Width if P=0.5	N
0.05	0.163	0.068	839
0.05	0.200	0.062	984
0.05	0.243	0.058	1134
0.05	0.300	0.055	1291
0.05	0.400	0.051	1476
0.06	0.163	0.081	583
0.06	0.200	0.075	683
0.06	0.243	0.070	786
0.06	0.300	0.065	897
0.06	0.400	0.061	1025

CI = confidence interval

Continuous Outcomes

Hypothesis testing: A sample size of 1052 achieves 90% power to detect a difference of -0.30 between the null hypothesis mean of 0.00 and the alternative hypothesis mean of 0.30 with an estimated standard deviation of 3.00 and with a significance level (alpha) of 0.05 using a two-sided one-sample t-test (Zar 1984; Machin et al, 2011) (Table 5).

Table 5: Sample Size for Mean Hypothesis Test at α=0.05

Power	$Mean_1$-$Mean_0$	Standard Deviation	Effect Size	N
0.80	0.25	2.0	0.125	505
0.85	0.25	2.0	0.125	577
0.90	0.25	2.0	0.125	673
0.80	0.25	3.0	0.083	1131
0.85	0.25	3.0	0.083	1294
0.90	0.25	3.0	0.083	1514
0.80	0.30	3.0	0.100	786
0.85	0.30	3.0	0.100	899
0.90	0.30	3.0	0.100	1052
0.80	0.30	2.0	0.150	351
0.85	0.30	2.0	0.150	401
0.90	0.30	2.0	0.150	469
0.80	0.40	2.0	0.200	199
0.85	0.40	2.0	0.200	227
0.90	0.40	2.0	0.200	265
0.80	0.40	3.0	0.133	444
0.85	0.40	3.0	0.133	507
0.90	0.40	3.0	0.133	593

Confidence Interval: A sample size of 1292 produces a two-sided 95% CI with a distance from the mean to the limits that is equal to 0.30 when the estimated standard deviation is 5.5 (Hahn and Meeker 2011) (Table 6).

Table 6: Sample Size 95% Confidence Interval for a Mean at α=0.05

Distance from the Mean[1]	Standard Deviation	N
0.1	1.5	865
0.2	3.5	1177
0.2	5.5	2906
0.3	3.5	526
0.3	5.5	1292

1. Distance from Mean to Limit is the distance from the confidence limit(s) to the mean. For two-sided intervals, it is also known as the precision, half-width, or margin of error.

The plan to enroll 1500 participants includes the expectation of increasing attrition over time. Analyses will be conducted with the data available at that time point and adjusted for missing values. This sample size is adequate to detect small effect sizes even with large amounts of variability for univariate statistics (one sample hypothesis test and CI) for both proportions and means. The sample size tables for each test or interval demonstrate sustained power to detect small to moderate effect sizes even with large amounts of attrition and show potential power at longitudinal time points with fewer observations.

8.6. Data Management

The electronic data capture (EDC) system for this study is OmniComm Systems, Inc, a web-based EDC system. It will be used to collect, monitor, and report clinical data as specified in

the protocol. Investigators or authorized staff will enter the data via a web-portal. All data collected via the eCRF will be reviewed by remote data monitors for clarity and completeness. Missing or unclear data will be queried according to the data management plan. The database and data management plan will be generated according to approved specifications. All patient reported outcomes data and questionnaires will be captured in the EDC, either patients will directly enter their responses into a patient data capture software system which will transfer data into the EDC or the site staff will enter in data from paper versions.

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed and maintained by the sponsor.

For the purposes of this study, analyses will be descriptive in nature and will be conducted using SAS (version 9.3 or higher). All variables will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges and standard deviations of continuous variables of interest, and proportions and frequency distributions for categorical variables. A Kaplan-Meier analysis will be performed on time-to-event outcomes such as death. In addition, as data are longitudinal, a repeated measures model of outcomes over time assessments may be considered.

No formal hypothesis testing is planned.

The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.7.1. EORTC QLQ-C30

The EORTC QLQ-C30 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. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms.

8.7.2. G8 Screening Tool

The G8 consists of 7 items based on the Mini-Nutritional Assessment and a single item covering the patient’s age. Patients falling below the cut-off of 14 points are recommended to complete a GA.

8.7.3. ADL

The ADL is a subscale of the Medical Outcomes Study (MOS) Physical Health. The MOS Physical Health Scale measures a broad range of physical functioning, with questions ranging from “Can you bathe and dress yourself?” to “Can you perform vigorous activities, such as running or lifting heavy objects?” Items are rated on a 3-point Likert scale measuring independence in performing the activity.

8.8. Quality Control

Investigators will be trained with an initial on-site visit to the clinic on the protocol, EDC system (i.e., eCRF), investigator site master file (ISMF), documentation, and any applicable study processes. Any new information relevant to the performance of this NIS will be forwarded to the medical staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of safety data, data integrity, and consistency. eCRFs for all included patients will be made available to the remote data monitor for review. A list of critical variables will be created as required elements for review during the remote data monitoring process. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

Monitoring visits may be made, if necessary, to monitor study process by Pfizer, Inc. or its delegate. In the event of a visit, direct access to original source data will be required for monitoring visits and/or inspections/audits, which will be carried out with due consideration for data protection and patient confidentiality.

Items routinely checked during on-site visits include:

- Documentation of the informed consent process
- Compliance with patient eligibility criteria
- Proper maintenance of records, such as study protocol
- Completed eCRFs
- Documentation of adverse events, and transmission of serious adverse events
- Identification of patients lost to follow up
- Study correspondence
- Compliance with Institutional review board (IRB)/ Independent ethics committee (IEC) approval requirements
- Review of the Investigator Site Master File

Archiving of the study documents will be performed accordingly to Pfizer standard operating procedures (SOPs).

8.9. Limitations of the Research Methods

The source data described in this protocol contain the inherent limitation of any current NIS, real world study. These studies have the potential for missing, inaccurate, or incomplete data. The limitations of the observational nature can result in methodological challenges in attributing causality to outcomes. The patient selection and the diagnostic or monitoring procedures are those applied per the usual treatment paradigm of the treating physician and

not dictated by the protocol. Heterogeneous patient populations could make the interpretation of the outcomes difficult. Hence, this study is intended for hypothesis generation, as opposed to hypothesis confirmation.

8.10. Other Aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/ IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with

the IRB/IEC should be retained in the Investigator Site Master File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the electronic case report form (eCRF) and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Table 7: Recording and Reporting of Safety Events

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of palbociclib or the time of the patient's informed consent if s/he is already exposed to palbociclib, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a

report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to palbociclib, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to palbociclib, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that palbociclib caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether palbociclib caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that palbociclib did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) palbociclib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to palbociclib (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to palbociclib prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with palbociclib, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to palbociclib in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single Reference Safety Document

The product label will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The product label should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are not part of any planned submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

12. REFERENCES

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14. LIST OF FIGURES

None

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- G8 (Geriatric Screening Tool): POLARIS STUDY VERSION 1 26OCT2016
- ADL Activities of Daily Living: POLARIS STUDY VERSION 1 26OCT2016

EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

G-8 Screening Tool

G8 Screening Tool

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss >3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI <19
		1 = BMI 19 to <21
		2 = BMI 21 to <23
		3 = BMI ≥23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
Age		0: >85
		1: 80–85
		2: <80
	Total score	0–17

POLARIS STUDY VERSION 1 26OCT2016

ADL Activities of Daily Living

Activities of Daily Living

Please check the circle that best applies to you. How much help do you get doing these daily activities?			
Activities	**No Assistance Needed**	**Partial Assistance Needed**	**Unable to do without Assistance**
1. Bathing	○ Able to bathe completely without assistance	○ Receives assistance in bathing only one part of the body(such as back or a leg	○ Receives assistance in bathing more than one part of the body or unable to bathe self
2. Dressing	○ Gets clothes and gets completely dressed without assistance(except for tying shoes)	○ Needs assistance; remains partially undressed without assistance	○ Unable to dress
3. Toileting	○ Receives no assistance (may use object for support such as cane, walker, or wheelchair or manages night bedpan or commode	○ Receives assistance in going to the toilet	○ Unable to use toilet without assistance
4. Transfer	○ Moves in and out of bed as well as in and out of chair without assistance (may use object for support such as cane or walker	○ Moves in and out of bed or chair with human assistance	○ Doesn't get out of bed or unable to transfer self
5.Continence	○ Controls urination and bowel movement by self	○ Has occasional "accidents"	○ Needs supervision for urine or bowel control or use catheter or colostomy
6. Feeding	○ Feeds self without assistance	○ Needs help in cutting meat or buttering bread, for example	○ Unable to feed self or is fed partly or completely by using tubes or intravenous fluids.