ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A171601

A PHASE II TRIAL ASSESSING THE TOLERABILITY OF PALBOCICLIB IN COMBINATION WITH LETROZOLE OR FULVESTRANT IN PATIENTS AGED 70 AND OLDER WITH ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER

Commercial agent(s): Palbociclib; (IND: exempt)

ClinicalTrials.gov Identifier: NCT03633331.

Study Chair
Mina S. Sedrak MD, MS
City of Hope Comprehensive Cancer Center
[redacted]

Study Co-Chair
Aminah Jatoi MD
Mayo Clinic
[redacted]

Community Oncology Co-Chair
[redacted]

Correlative Study Co-Chair
[redacted]

Pharmacogenomics Study Co-Chair
[redacted]

Imaging Co-Chair
[redacted]

Pharmacokinetics Study Co-Chair
[redacted]

Breast Committee Study Co-Chair
[redacted]

Study Co-Chair
[redacted]

Cancer in the Elderly Committee Co-Chairs
[redacted]

Breast Committee Co-Chairs
[redacted]

Primary Statistician
[redacted]

Secondary Statistician
[redacted]

Data Manager
[redacted]

Protocol Coordinator
[redacted]

In memory of Dr. Arti Hurria

Participating NCTN Groups:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/ SWOG

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A171601 Nursing Contact

[redacted]

A171601 Pharmacy Contact

[redacted]

Alliance Biorepository at Mayo Clinic

[redacted]

IROC

[redacted]

University of Pittsburgh Cancer Institute

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Appropriate Alliance Biorepository
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions by phone or email : [redacted], or [redacted].	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
Institutions will order the following supplies from the CTSU Operations Office: Questionnaire booklets. Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted], or [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		

A PHASE II TRIAL ASSESSING THE TOLERABILITY OF PALBOCICLIB IN COMBINATION WITH LETROZOLE OR FULVESTRANT IN PATIENTS AGED 70 AND OLDER WITH ESTROGEN RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER

Eligibility Criteria (See Section 3.2)

Estrogen receptor positive and/or progesterone receptor (PR) positive, HER2 negative metastatic breast cancer See 3.2.1
Measurable disease or non-measurable disease See 3.2.2
Planning to begin palbociclib for metastatic disease. Patients should have failed one prior line of endocrine therapy. See 3.2.3
No prior therapy with a CDK inhibitor See 3.2.4
Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE Grade ≤ 1 (except alopecia) or to baseline toxicities prior to previous therapy or surgical procedures. See 3.2.5
No untreated brain metastases See 3.2.6
No known interstitial lung disease. See 3.2.7.
No second malignancies other than non-melanoma skin cancers or cervical carcinoma in situ See 3.2.8.
No active infection requiring treatment with antibiotics See 3.2.9.
Patients must be able to swallow and retain oral medication See 3.2.10.
Patient Age: ≥ 70 years See 3.2.11.
ECOG Performance Status 0, 1 or 2 See 3.2.12.
Patients must be able to read and comprehend English or Spanish See 3.2.13

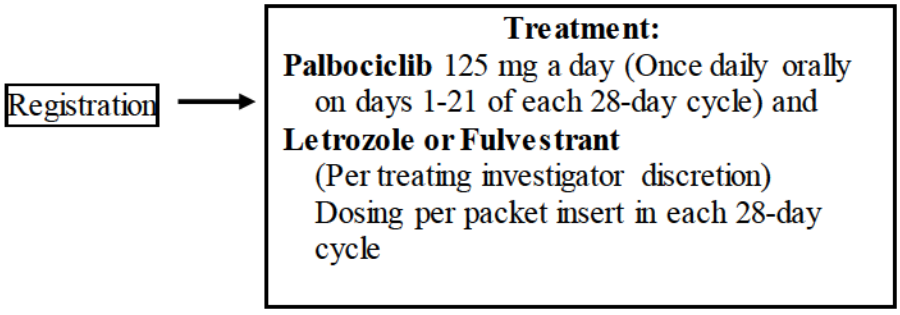
Required Initial Laboratory Values

ANC	≥ 1500/mm³
Platelet count:	≥ 100,000/mm³
Creatinine:	≥ 30 ml/min*
Total serum bilirubin	≤ 1.5 ULN (< 3 ULN if Gilbert's disease)
AST and/or ALT	≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present)
Alkaline phosphatase	≤ 2.5 x ULN (≤5 x ULN if bone or liver metastases present)

* Calculated using the Cockcroft-Gault formula

Schema

1 cycle = 28 days



Continue protocol treatment until unacceptable toxicity or disease progression

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

This protocol addresses a key research priority of the Cancer and Aging Research Group, National Cancer Institute, National Institute on Aging, and the Institute of Medicine: the assessment of cancer therapy in older adults [6, 7] Palbociclib is a novel drug with the potential to change the treatment of metastatic breast cancer- a primary disease of older adults. The combination of palbociclib and endocrine therapy (the aromatase inhibitor, letrozole, or fulvestrant) is associated with an improvement in progression-free survival (PFS) compared to endocrine therapy alone.[1,2] However, a small proportion of patients enrolled in these studies were age 75 and older. The pivotal trial of palbociclib reported in the package insert notes that only 37 patients (44%) were ≥65 years of age and 8 patients (10%) were ≥75 years of age. The goal of this study is to fill this gap in knowledge by utilizing a phase II design to examine the tolerability of palbociclib and endocrine therapy among older adults age 70 and older with estrogen receptor positive, HER2 negative breast tumors. A comprehensive cancer-specific geriatric assessment which includes an evaluation of functional status, other medical conditions, cognitive function, nutritional status, social support, psychological state, and a review of medications will be included, as well as an assessment of adherence.

1.1 Aging and a Decrease in Physiologic Reserve: Rationale for Studying Cancer Therapy in Older Adults

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.[8, 9] The age-related physiological decline in organ systems typically begins in the 3rd decade of life and is not evident at times of rest but becomes most apparent when the body is stressed.[10] Both cancer and cancer treatment can be considered a physiological stressor, and age-related decreases in physiologic reserve may affect tolerance to cancer treatment.

A number of age-related changes in drug absorption, distribution, metabolism, and excretion with aging may contribute to differences in treatment tolerance between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[11, 12] With the increased use of oral therapy, medication compliance is an important issue as well.[13] As a person ages, body composition changes, with an increase in body fat and decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for hydrophilic drugs. In the population of older adults with cancer, malnutrition and hypoalbuminemia may result in an increased concentration of drugs that are albumin-bound.[14]

Hepatic mass and blood flow also decrease with age.[8] The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.[15] In a study of 226 patients, the cytochrome P-450 content in liver biopsy samples decreased by approximately 30% in patients over the age of 70.[16] Renal function also declines with age, and renal insufficiency is common in older adults.[17, 18]

A progressive reduction in the functional reserve of various organ systems may alter the pharmacokinetics of anti-cancer therapies[11, 19] and increase the susceptibility of older individuals to complications of treatment.[14, 20-22] Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiotoxicity, neurotoxicity, mucositis, and hematologic toxicities.[23]

1.2 Factors Other than Chronological Age that Impact Drug Tolerance

Aging is a heterogeneous process. While certain declines in organ function are universal as the human body ages, the rate of this decline and the consequences of this decline on everyday function proceeds at a unique pace in each individual. Therefore, chronological age tells us

relatively little about the specific individual. A more detailed evaluation of an older adult patient is needed in order to capture factors other than chronological age that predict for morbidity and mortality. A comprehensive geriatric assessment may serve this purpose. The comprehensive geriatric assessment includes an evaluation of functional status, co-morbid medical conditions, cognitive function, nutritional status, social support and psychological state, and a review of medications[3,4]. Conclusions from several studies are emerging regarding the benefits of performing a comprehensive geriatric assessment for older patients with cancer.

1. Factors evaluated in a comprehensive geriatric assessment predicts survival. [24]

2. Factors evaluated in a comprehensive geriatric assessment predicts toxicity to chemotherapy. [25]

3. A comprehensive geriatric assessment uncovers problems not detected by routine history and physical in initial consultation and follow-up care. [26]

4. Patients undergoing a comprehensive geriatric assessment and intervention based on the results had improved pain control. [27]

5. A comprehensive geriatric assessment and intervention improves an older patient's mental health and well-being.[27]

6. Consensus guidelines recognize the benefits and recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient.[28]

1.3 Palbociclib

Palbociclib is a reversible, selective, cyclin dependent kinase (CDK) 4/6 inhibitor that is able to stop the normal process of the cell cycle as the cell travels from G1 phase to S phase1. In the absence of palbociclib, these kinases will phosphorylate the retinoblastoma (Rb) protein to cause a release of transcription factors which allows the cell to move through the cell cycle, thus allowing the growth of cancerous cells[1]. When palbociclib inhibits CDK4 and CDK6, the retinoblastoma protein is arrested at the G1 phase, prohibiting "S-phase entry and cell growth" of the cancerous cells[29].

1.4 A Rationale for Combining Palbociclib and Endocrine Therapy

Palbociclib in combination with endocrine therapy compared to endocrine therapy alone improves progression-free survival. Data from the PALOMA-1 trial demonstrates the efficacy of palbociclib with letrozole in the first line treatment of estrogen receptor positive metastatic breast cancer.[1] In this randomized open-label phase II study, 165 women ranging from ages 54-72 had advanced estrogen receptor positive and HER-2 negative breast cancer. One cohort of women (mean age 65) was enrolled because of their estrogen receptor positive and HER2-negative breast cancer, whereas a second cohort (mean age 62.5) was enrolled because they also had cancers with amplification of *CCND1* and/or loss of P16. These cohorts received either letrozole alone (orally 2.5mg/day) or letrozole (orally 2.5mg/day) with palbociclib (orally 125 mg/day for three weeks on and one week off). Eighty-four patients were assigned to the palbociclib-letrozole group and 81 to letrozole alone. The median progression-free survival was 20.2 months for the palbociclib and letrozole arm, compared to 10.2 months for letrozole alone. Common side effects for palbociclib with letrozole compared to letrozole alone (Table 1) were: grade 3-4 neutropenia (54% vs. 1%), leukopenia (19% vs. 0%), and fatigue (4% vs. 1%). Four percent of patients receiving palbociclib with letrozole experienced a pulmonary embolism. Among patients in the palbociclib and letrozole group, 13% discontinued due to side effects whereas only 2% of the letrozole group discontinued the study.

Table 1: Common Adverse Reactions with an Incidence of ≥ 5% in Patients who Received Palbociclib plus Letrozole or Letrozole Alone in PALOMA-1 Study[1]

	Palbociclib plus Letrozole (N=83)		Letrozole (N=77)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any adverse event	49 (59%)	14 (17%)	16 (21%)	0
Neutropenia	40 (48%)	5 (6%)	1 (1%)	0
Leukopenia	16 (19%)	0	0	0
Anemia	4 (5%)	1 (1%)	1 (1%)	0

*Data are in n (%) unless otherwise specified

PALOMA-2[30] - which was designed to expand efficacy and safety data for palbociclib and letrozole treatment - had a sample size of 666 postmenopausal women with ER-positive, HER2-negative, breast cancer. In PALOMA-2, the median age of patients receiving palbociclib-letrozole was 62 with a range from 30-89, with only 39.3% of participants age 65 and over with no published information for patients older than 75. Among patients receiving placebo and letrozole the median PFS was 14.5 months (95% CI 12.9-17.1). This efficacy improved with palbociclib-letrozole to 24.8 months (95% CI 22.1-Not reached). The most common grade 3 or 4 adverse events were neutropenia with 66.4% of patients treated with palbociclib-letrozole experiencing this compared to 1.4% in the placebo-letrozole group. Leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%) and fatigue (1.8% vs. 0.5%) were also reported.

Further support for use of palbociclib in conjunction with hormone therapy was carried out in the PALOMA-3 trial.[2] This phase III trial included 521 patients randomized into 2 groups: palbociclib and fulvestrant (N=347) or fulvestrant alone (N=174). Patients were eligible to participate in this study if they were estrogen receptor positive. Patients enrolled in this study could have had prior endocrine therapy (38.8% first line, 25.5% second line, 10.9% third line and above). In addition, patients were allowed one prior line of chemotherapy. The median progression-free survival was 9.2 months for the palbociclib and fulvestrant arm, compared to 3.8 months for fulvestrant alone. Common side effects for palbociclib and fulvestrant compared to fulvestrant alone were: neutropenia (62% vs. 6%), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), fatigue (2.0% vs. 1.2%), and febrile neutropenia (0.6% for both groups). Among patients in Group 1, 2.6% discontinued the study while 1.7% of patients in Group 2 discontinued due to side effects.

1.4.1 Age Specific Data from PALOMA-1, PALOMA-2 and PALOMA-3

Limited evidence exists to guide therapy with palbociclib and endocrine therapy in older adults. In PALOMA-1, the mean age of patients was 64 with a range from 54-72. In PALOMA-2, the median age of patients receiving palbociclib-letrozole was 62 with a range from 30-89, with only 39.3% of participants age 65 and over with no published information for patients older than 75. In PALOMA-3, the mean age of patients was 64 with a range from 29 to 88. In PALOMA-3, only 25% of the participants were age 65 and over. Review of the data obtained from 165 patients in the PALOMA-1 trial, as well as the 521 patients in the PALOMA-3 trial, did not show any apparent differences in systemic exposure related to age. A subgroup analysis of the efficacy and safety of first-line palbociclib plus letrozole compared with letrozole alone in patients in the PALOMA-1 study evaluated 165 postmenopausal women. Of the 76 patients age 65 and older, 37 were treated with palbociclib and letrozole, and the remainder received letrozole alone. Among patients receiving palbociclib and letrozole the median PFS for patients age 65 and over was 26.6 months (95% CI 12.6-NR) in comparison to 7.7 months (95% CI 3.7-10.9) for patients who

received letrozole alone. Grade 3-4 neutropenia occurred in 56.8% of patients receiving palbociclib and letrozole (compared to 2.7% in patients with letrozole alone). In addition, grade 3-4 leukopenia occurred in 29.7% of the patients receiving palbociclib and letrozole, and grade 3-4 fatigue was reported in 10.8% of patients receiving palbociclib and letrozole. Neither of these adverse events occurred in any patients taking letrozole alone.[31]

Another subset analysis of the PALOMA-1 study evaluated the time to onset of neutropenia, leukopenia, anemia, and thrombocytopenia. They found that 97.9% of all adverse events occurred within the first 6 months and stayed relatively stable or decreased in incidence over time. Within the first 6 months, 69.5% of the 95 participants presented with neutropenia, 33.7% with leukopenia, and 22.1% with anemia. The median time to onset for neutropenia was 20 days, for leukopenia was 36 days, for anemia was 168 days, and for thrombocytopenia was 140 days. They did not see any evidence of specific cumulative or late onset of toxicity with treatment on palbociclib and letrozole.[32]

1.4.2 Filling a Gap in Knowledge

Palbociclib and endocrine therapy is emerging as a novel treatment for estrogen receptor positive metastatic breast cancer. A gap in knowledge specifically exists with regard to the tolerability of this combination in adults age 70 and over. This is an important research area, since cancer is a disease associated with aging. Twenty percent of patients with breast cancer are age 70 and older. This phase II study will evaluate the safety and tolerability of the combination of palbociclib and letrozole or fulvestrant in patients age 70 and over, as well as describe the full toxicity profile, estimate the objective response rate and clinical benefit, as well as survival. A geriatric assessment and measures of adherence will be included within the study. Overall our goal is to close this gap in knowledge in older adults with metastatic breast cancer who may derive significant benefit from this novel treatment option.

1.4.3 Rationale for the Study

Limited evidence exists to guide therapy with targeted agents in the older adult population because older adults have been under-represented in clinical trials. Adults age 70 and older make up only 20% of subjects enrolled in FDA registration trials but 46% of all patients with cancer diagnoses. Dose-finding studies specifically in older adults are not routinely performed. This is despite changes in drug metabolism, absorption, and distribution with increasing age. The combination of palbociclib and endocrine therapy is a novel treatment approach for postmenopausal women with estrogen receptor positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. The combination significantly improves progression-free survival compared to endocrine therapy alone. However, these studies primarily focused on women less than age 75. For example, the randomized phase II trial (PALOMA-1) of palbociclib and letrozole compared to letrozole alone (mean age 63 and 64, respectively) only included 8 patients age 75 and older, and the phase III trial (PALOMA-3) of palbociclib and fulvestrant compared to fulvestrant alone (mean age 57 and 56, respectively) included only 25% of participants age 65 and older, while not reporting on participants age 75 and older.[1,2] In PALOMA-2, the median age of patients receiving palbociclib-letrozole was 62 with a range from 30-89, with only 39.3% of participants age 65 and over with no published information for patients older than 75. In addition, the pivotal trial of palbociclib and letrozole reported in the package insert notes that 37 patients (44%) were $\geq$ 65 years of age and only 8 patients (10%) were $\geq$ 75 years of age.

The most common adverse events of palbociclib in combination with endocrine therapy are neutropenia, leukopenia, and fatigue. In particular, in PALOMA-1 patients receiving the

combination palbociclib and letrozole experienced grade 3 or 4 neutropenia (54%), leukopenia (19%), or fatigue (4%). In PALOMA-3, patients receiving palbociclib and fulvestrant experienced grade 3 or 4 neutropenia (62%), leukopenia (25.2%), or fatigue (2%). The package insert specifically warns of potential febrile neutropenia and infection; although, neutropenic fever is very rare with the combination (PALOMA-1 with 0%, PALOMA-3 with 0.6%). In addition, the package insert includes warning of thromboembolism (PALOMA-1 with 4%, PALOMA-3 with 0%). These side effects are of particular concern in older adults. In particular, there is a decrease in bone marrow reserve with aging, hence amplifying the potential risk of neutropenia and myelosuppression. Furthermore, older adults often have other co-morbid medical conditions which may predispose them to thromboembolism thereby increasing the risk. Because of this, a definitive study in the older adult population will diminish any reservations oncologists may have in prescribing palbociclib with letrozole or fulvestrant and can provide guidance regarding the dosing and toxicity management in older adults.

This is an open label, single arm, phase II study of the combination of palbociclib and letrozole or fulvestrant in 88 patients age 70 or over with estrogen receptor positive, HER2 negative metastatic breast cancer. The primary goal of this study is to estimate the safety and tolerability (adverse event rate) of the combination of palbociclib and endocrine therapy in older adults with estrogen receptor positive, HER2 negative metastatic breast cancer. Secondary aims are to describe the full toxicity profile, describe dose modifications, evaluate disease response in this population, evaluate patient adherence and treatment perspective, and to explore factors other than chronologic age that predict toxicity using a cancer-specific geriatric assessment. Correlative studies in this proposal will also aim to evaluate circulating markers of inflammation as potential markers predictive of toxicity or physical function as assessed by the cancer-specific geriatric assessment, and to examine single nucleotide polymorphisms (SNPs) in cell cycle genes and genes that metabolize palbociclib.

1.5 Measurement of Sarcopenia

1.5.1 Background and Methods

Age-related loss of muscle mass and function, otherwise known as sarcopenia, is highly prevalent in older adults and associated with functional impairment, disability, loss of independence, and mortality.[33-35] Losses in skeletal muscle mass and strength are apparent as early as the 4th decade of life and progress linearly with increasing age.[36] Sarcopenia in older adults with cancer is additionally complicated by cancer-related cachexia and frailty.[37,38]The elevated inflammatory response and alterations in metabolism related to cancer cachexia lead to further losses of muscle mass [39,40] There is a high prevalence of sarcopenia in adults with breast cancer, particularly in older adults (~63%).[41] Sarcopenia has been associated with increased grade 3/4 chemotherapy toxicity, hospitalizations, and adverse events in adults with metastatic breast cancer undergoing taxane-based chemotherapy [42] The presence or absence of sarcopenia may help explain the inter-individual variability in treatment tolerability of older adults with cancer and could ultimately be used to individualize treatment planning. Although there have been several studies examining the association of sarcopenia and chemotherapy, this unique small study will explore its association with targeted therapy in older adults. This proposal also aims to evaluate the impact of sarcopenia on targeted therapy toxicity and adverse events in older adults with breast cancer undergoing treatment with palbociclib and endocrine therapy.

Practical and precise measurement approaches have been developed to quantify body composition in patients with cancer using CT images acquired during routine care that

require minimal additional resource allocation.[43] The L3 landmark from cross-sectional imaging has been identified as the strongest predictor of whole body fat and fat-free mass when compared to dual-energy x-ray absorptiometry (DXA).[43] The advantage of using advanced imaging modalities, such as CT imaging, is the ability to provide additional qualitative measurements of muscle and fat beyond purely quantitative measures [44]

1.6 Quality of Life Questionnaires: EuroQol 5D 3L and EQ Visual Analog Scale (EQ VAS)

In addition to the reporting of symptoms, understanding how quality of life may be affected by palbociclib and hormonal therapy in the metastatic setting in older patients has not been evaluated previously and will add important information to this study. The EQ-5D (Appendix V) is a measure of health status for use in evaluating health and healthcare. The EQ-5D-3L is comprised of 2 pages: the EQ-5D descriptive system (page 1) and the EQ visual analogue scale (EQ VAS) (page 2). It provides a simple descriptive profile of five functional dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It generates a single index value for health status on which full health is assigned a value of 1 and death a value of 0. Thus, the index can be used to obtain a utility for these dimensions for use in economic analyses. The EQ-5D has been specially designed to complement other quality of life measures such as the SF-36, or cancer-specific measures. Each dimension has three levels designated simply as 'no problem', 'some problem', or 'extreme problem', with patients checking the level most descriptive of their current level of function on each dimension. Five dimensions, each with three levels, yield 243 possible distinct health states comprising the classification system. The classification system has been assigned different standardized scores derived through population-based samples of respondents who assign values to subsets of the 243 states using the anchoring labels noted above. For example, health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. A set of valuation weights has thus been derived from a U.S. sample.[45] The Agency for Healthcare Research and Quality has funded a study to develop definitive weights. EQ-5D is designed for self-completion by patients and has been used extensively in mailed surveys. It is cognitively simple, taking no more than a few minutes to complete.

1.7 PRO-CTCAE

We will evaluate how well symptoms reported by patients correlate/agree with those compared to what is reported in clinic using traditional AE evaluations.

Patient-reported outcomes (PRO) are an important part of new drug evaluation and may play a role in regulatory approval of novel agents in oncology [46]. PROs can be the consequences of disease and/or its treatment as reported by the patient. PROs are evaluated through the use of questionnaires developed to assess topics a patient can report about his or her own health and are often completed electronically. This includes symptoms, physical functioning, and mental health.

The current standard mechanism for reporting toxicities in cancer research is clinician-only reporting using items from the National Cancer Institute (NCI) CTCAEs. In multiple studies, PRO measures have improved the predictive accuracy of clinician CTCAE reporting. In a prospective study including lung cancer patients' PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation [47]. Although PROs have been well validated [48, 49, 50, 51], these examinations have been minimally evaluated for feasibility and accuracy in an older patient group and will meaningfully add to the data collection on this study.

We will focus our PROs on side effects most commonly reported in prior studies with palbociclib and hormonal therapy and which of are of most interest, including all symptoms listed in Appendix VI.

All surveys will be given to patients on paper, at the same time points as in-clinic evaluations through cycle 6, unless patients come off study prior to cycle 6. We will use the PRO-CTCAE items developed by the National Cancer Institute in order to allow patients to self-report the above symptomatic adverse events. The primary purpose of the inclusion of PRO-CTCAE is to evaluate the performance and agreement of patient-reported outcomes with those collected as clinician-reported CTCAEs.

2.0 OBJECTIVES

2.1 Primary Objective

To estimate the safety and tolerability (adverse event rate) of the combination of palbociclib and letrozole or fulvestrant in adults age 70 or older with estrogen receptor-positive, HER2-negative metastatic breast cancer.

2.2 Secondary objectives

2.2.1 To describe the full toxicity profile including all grade 2 and higher adverse events (per NCI CTCAE v.5.0), specifically estimating the rate of grade 2 and higher myelosuppression (neutropenia, leukopenia, thrombocytopenia, and anemia), neutropenic fever, GI side effects (nausea, diarrhea, decreased appetite, vomiting, mucositis-oral), fatigue, neuropathy, and thromboembolism.

2.2.2 To describe rates of dose reductions, dose holds, and hospitalizations.

2.2.3 To estimate median time to treatment failure, including progression free survival and overall survival.

2.2.4 To estimate the rate of adherence to palbociclib, letrozole and fulvestrant.

2.2.5 To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment.

2.2.6 To describe the results of the Was It Worth It (WIWI) Questionnaire and the Overall Treatment Utility (OTU).

2.2.7 To determine the degree of agreement between patient-reported AEs using PRO-CTCAE measures and those reported using traditional collections for AEs.

2.2.8 To examine the association between sarcopenia and the development of toxicity and adverse events.

2.3 Correlative science objectives

2.3.1 To explore the association between baseline chronic inflammatory mediator levels and development of adverse events.

2.3.2 To explore the association between baseline chronic inflammatory mediator levels and treatment modification.

2.3.3 To explore the association between baseline chronic inflammatory mediator levels and baseline physical function as assessed by the cancer-specific geriatric assessment.

2.3.4 To explore the association between baseline chronic inflammatory mediator levels and decline in physical function as assessed by the cancer-specific geriatric assessment.

2.3.5 To explore the correlation between inherited single nucleotide polymorphisms (SNPs) in cell cycle pathway genes and in genes that metabolize palbociclib and treatment efficacy and toxicity (clinical outcomes) in elderly patients undergoing combined endocrine therapy plus palbociclib for estrogen receptor positive, HER2 negative metastatic breast cancer.

2.3.6 To explore whether genes in *CYP19A, CYP2A6* and *ESR1* will also correlate with treatment efficacy and toxicity (clinical outcomes) in elderly patients undergoing combined endocrine therapy plus palbociclib for estrogen receptor positive, HER2 negative metastatic breast cancer.

2.3.7 To refine a population pharmacokinetic model using NONMEM for palbociclib based on that of Sun and Wang (ESMO Poster Presentation 462P 2014) taking account of relevant intrinsic and extrinsic factors.

2.3.8 To determine the intrapatient and interpatient variability of palbociclib exposure (AUC) in older breast cancer patients receiving palbociclib plus letrozole/fulvestrant.

2.3.9 To explore the exposure (AUC/C_{max}) toxicity (neutropenia, thrombocytopenia) relationship for palbociclib when combined with letrozole/fulvestrant in older breast cancer patients.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. **Please note that the Study Chair cannot grant waivers to eligibility requirements.**

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Concomitant medications:

  Chronic concomitant treatment with strong inhibitors of CYP3A is strongly discouraged on this study. Patients on strong CYP3A inhibitors must discontinue the drug prior to registration on the study. See section 8.1.10 for more information.

  Chronic concomitant treatment with strong CYP3A inducers is strongly discouraged. Patients must discontinue the drug prior to the start of study treatment. See section 8.1.11 for more information.

  Chronic concomitant treatment with CYP2A6 substrates is strongly discouraged for patients who are being treated with letrozole. Patients must discontinue the drug prior to the start of study treatment. See section 8.1.12 for more information.
- Life expectancy of less than 6 months

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease: Estrogen receptor positive and/or progesterone receptor (PR) positive, HER2 negative metastatic breast cancer.** Histologic confirmation is required.

___ **3.2.2 Measurable disease or non-measurable disease (see Section 11.3)**

___ **3.2.3 Planning to begin palbociclib for metastatic disease. One prior line of endocrine therapy and/or chemotherapy for metastatic disease is allowed.**

Patients may begin or have already begun endocrine therapy before they start palbociclib treatment, but no more than two weeks prior to registration.

___ **3.2.4 No prior therapy with a CDK inhibitor.**

___ **3.2.5 Resolution of all acute toxic effects of prior therapy or surgical procedures to CTCAE Grade ≤ 1 (except alopecia) or to baseline toxicities prior to previous therapy or surgical procedures, prior to registration.**

___ **3.2.6 No untreated brain metastases.** Patients with treated brain metastases must have completed treatment with steroids to be eligible.

___ **3.2.7 No known interstitial lung disease.**

___ **3.2.8. No second malignancies other than non-melanoma skin cancers or cervical carcinoma in situ. However, patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.**

___ **3.2.9 No active infection requiring treatment with antibiotics.**

___ **3.2.10 Patients must be able to swallow and retain oral medication.**

___ **3.2.11 Patient Age: ≥ 70 years**

___ **3.2.12 ECOG Performance Status 0, 1 or 2.**

___ **3.2.13 Patients must be able to read and comprehend English or Spanish.**

___ **3.2.14 Required Initial Laboratory Values:**

Absolute neutrophil count (ANC)	≥ 1500/mm^3 (1.5 x 10^9/L)
Platelet count:	≥ 100,000/mm^3 (100x 10^9/L)
Creatinine clearance:	≥ 30 ml/min*
Total serum bilirubin	≤ 1.5 ULN (< 3 ULN if Gilbert's disease)
AST and/or ALT	≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present)
Alkaline phosphatase	≤ 2.5 x ULN (≤ 5 x ULN if bone or liver metastases present)

* Calculated using the Cockcroft-Gault formula

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted].

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted].

4.2 CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;

- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Protocol Specific Requirements for A171601 Site Registration

- Evidence of Geriatric Assessment Training, as described in Section 15.0

IROC credentialing:

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted]. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *[Alliance]*, and protocol number *[A171601]*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.5 Credentialing

See Section 15.0 for credentialing requirements for Geriatric Assessment Training.

4.3 Patient Registration Requirements

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient completed booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets in English and Spanish can be ordered by downloading and completing the CTSU supply request form (located under the site registration section of the CTSU protocol specific website) and submitting the form through the CTSU regulatory portal. Samples of the booklets in English are found in Appendices II-VII and electronic versions of the booklets in Spanish are available on the Alliance and CTSU web sites. These are to be used for reference and IRB submission only. They are not to be used for patient completion.

Protected Health Information: Whole blood samples collected for the pharmacokinetics sub-study A171601-PP1 will be sent directly to the University of Pittsburgh Cancer Center. These samples will be labeled with patient initials, study ID and collection date/time.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs

registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- Site staff have completed the Geriatric Assessment training described in Section 15.0.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Sub studies described in Section 14.0

There are 3 sub studies within Alliance A171601. These studies **must** be offered to all patients enrolled on Alliance A171601 (although patients may opt to not participate). These sub studies do not require separate IRB approval. The sub studies included within Alliance A171601 are:

- Circulating markers of inflammation as potential markers predictive of toxicity among elderly patients enrolled to Alliance A171601: Alliance A171601-ST1 (Section 14.1)
- Genetic determinants of Palbociclib Efficacy and toxicity in the elderly: Alliance A171601-ST 2 (Section 14.2)
- Population Pharmacokinetics of Palbociclib: Alliance A171601-PP1 (Section 14.3)

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory studies described above.," Question #1 in the model consent, they have consented to participate in the sub studies described in Section 14.1 , Section 14.2 and Section 14.3. The patient should be registered to Alliance A171601 -ST1, A171601-ST2 and A171601-PP1 at the same time they are registered to the treatment trial (A171601). Samples should be submitted per Section 6.2.

4.6 Grouping Factor

4.6.1 Age 70-74 vs. ≥75

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals:

To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical, concomitant medications and baseline adverse event assessment.

To be completed ≤ 42 DAYS before registration: CT and bone scan, or PET scan

	Prior to registration	Cycles 1 and 2		Day 1 of every cycle starting with Cycle 3 for year 1 of treatment*	Every 3 mths from year 2 until end of treatment(+/-8 days)	At end of protocol treatment†
		Day 1*	Day 15*			
Tests and Observations						
History and Physical	X	X		X	X	
Adherence evaluation		A		B	X	
Adverse Event Reporting		X	X	X	X	X
PRO-CTCAE		X	X	X(1)		X(2)
Concomitant medications		X	X	X	X	
Geriatric Assessment		C		B		X(2)
EQ-5D-3L		X		X(1)		X(2)
Was It Worth It and Overall Treatment Utility						X
Laboratory Studies						
CBC, Differential, Platelets	X	X**	X	X	X	
CMP***	X	X**	X	X	X	
Staging						
CT chest/abd+/-pelvis or PET	X			D	X	
Bone Scan, Whole Body	X(3)			D	X	
Whole Blood and Plasma	**Correlative studies for patients who consent to participate** *To be collected at the timepoints described in Section 6.2*					

* +/- 2 days. 1 cycle = 28 days. (All Day 1 baseline assessments may be completed any time after registration but before treatment. H&P need not be repeated for Day 1 if done within a 30 day window prior to Day 1 of Cycle 1.)

** Need not be repeated if done within the last 7 days

*** CMP includes electrolytes (sodium, potassium, chloride, bicarbonate), renal function (blood urea nitrogen and creatinine) liver function tests (AST, ALT, alk. phos., total bilirubin, direct bilirubin only if clinically indicated), total protein, albumin, and calcium

† At the end of protocol treatment patients will complete the Geriatric Assessment and the end of treatment booklet. Patients will then be followed every year for survival only, up to 5 years

1 PRO-CTCAE and EQ-5L-3D required only for the first 6 cycles of protocol therapy during the first year of treatment

2 Does not need to be repeated if done within the last 30 days.

3 Radionuclide bone scan is not required if baseline PET scan was done. Bone scan after baseline is required only if indicative of metastases at baseline or if signs or symptoms suggestive of metastases development.

A End of cycle 1 and 2

B Day 1, Cycle 4 only

C Cycle 1 only

D Day 1 of Cycle 4 (+/- 2 weeks), then every 12 weeks (+/- 2 weeks) until end of treatment. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. See Section 6.3 for instructions on submission of images.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the Case Report Forms tab.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted]

- **Patient-completed questionnaire booklets** for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of the booklets in English are found in Appendices II-VII and electronic versions of the booklets in Spanish are available on the Alliance and CTSU web sites, for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into Rave.

6.1.3 Data Quality Portal:

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.1.4 Supporting documentation

This study requires supporting documentation for diagnosis, response, progression and survival. Supporting documentation will include pathology and imaging reports and must be submitted at the following time points:

Baseline: For patients with measurable disease only, pathology and imaging reports.

At Progression and response: Imaging reports and/or clinic notes, based on standard RECIST criteria.

All supporting documentation should be de-identified according to institutional standards prior to upload into RAVE.

6.2 Specimen collection and submission

For patients registered to substudy A171601-ST1, A171601-ST2 and A171601-PP1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A171601-ST1, A171601-ST2 and A171601-PP1, although patient participation is optional. Biomarker, pharmacogenetics studies and pharmacokinetic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, plasma and whole blood will be collected at the following time points for these studies: Collection of plasma for toxicity biomarker correlative studies will coincide with the Geriatric assessment on cycle 1 day 1, and prior to cycle 4.

For all patients registered to A171601 ST1, A171601- ST2 and A171601-PP1, submit the following:					
	Prior to Treatment	**Cycles 1 & 2 Day 15 (Prior to treatment)**	**Prior to Cycle 4**	**Storage/ Shipping conditions**	**Submit to:**
Whole Blood[1] (EDTA/lavender top)	10 mL		10 mL	Cool pack/ship over night	Mayo BAP Freezer
Whole Blood[2] (EDTA/lavender top)	10 mL			Cool pack/ship over night	Mayo BAP Freezer
Plasma from Whole Blood[3] (EDTA/lavender top)	5 mL	5 mL		Dry ice/ ship over night	University of Pittsburgh

1 Whole blood for Plasma to be used for biomarker analyses described in Section 14.1.

2 Whole blood to be used for pharmacogenomic analyses described in Section 14.2.

3 Pharmacokinetic analyses described in Section 14.3. Patients will be asked to complete a pharmacokinetics questionnaire (Appendix IX) these visits (Baseline, Cycles 1 &2 Day 15, prior to treatment). The questionnaire can be completed before or after the blood draw. A copy of the questionnaire will be sent by site staff along with the samples to the University of Pittsburgh. Questionnaire responses are to be entered into Rave by site staff.

Note: Samples for A171601- PP1 substudy are only required for patients who are registered (and consent to participate in the substudies) after Update 1. Patients enrolled prior to the release of Update 1 will not be asked to provide additional samples.

6.2.1 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and

training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted].

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A171601), Alliance patient number, patient's initials, date and type of specimen collected (e.g., serum, whole blood).

When specimens are time-sensitive, and/or are required for communication of test results back to institutions and patients, they should be labeled with patient initials and date of procurement, in addition to protocol number, Alliance patient number and specimen type. Specimens that are not time-sensitive, and/or are not submitted for the purpose of performing an integral test that will be reported back to patients, should not include patient initials or date of procurement.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Specimens for the A171601- ST1 and A171601-ST2 sub-studies should be shipped Monday through Friday marked for Saturday delivery. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays.

Specimens for the A171601-PP1 substudy should be sent to the following address:

[redacted]

All other specimens should be sent to the following address:

[redacted]

6.2.2 Whole Blood sample submission for plasma (A171601-ST1)

For patients who consent to participate, whole blood collected for plasma samples will be used for the biomarker analyses described in Section 14.1.

For EDTA plasma, collect 10 mL of whole blood by standard venous phlebotomy into the EDTA tube, prior to treatment and prior to cycle 4. The tube should be inverted several

times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository (Mayo BAP). The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

Label samples with the following identification:

1) Procurement date/time of collection
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A171601-ST1)
5) Specimen type

The 10ml of blood can be collected in one 10ml tube, or two 5ml tubes or three 3ml tubes, as long as the final volume is ~10ml.

6.2.3 Whole blood submission for pharmacogenomic studies (A171601-ST2)

For patients who consent to participate, whole blood samples will be used for the pharmacogenomic studies described in Section 14.2. This sample should be collected prior to the initiation of protocol treatment.

The following bio specimens will be collected at baseline:

Collect 10 mL of whole blood by standard venous phlebotomy into the EDTA tube. The tube should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight shipping to the Alliance Biorepository (Mayo BAP). The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

Label samples with the following identification:

1) Procurement date/time of collection
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A171601-ST2)
5) Specimen type

The 10ml of blood can be collected in one 10ml tube, or two 5ml tubes or three 3ml tubes, as long as the final volume is ~10ml.

6.2.4 Plasma submission for pharmacokinetic studies (A171601-PP1)

For patients who consent to participate, blood samples will be used for the pharmacokinetic analyses described in Section 14.3.

Plasma from Whole Blood in EDTA Lavender Top Tube:

Prior to receiving protocol therapy on Cycle 1 day 1 , Cycle 1 Day 15, and Cycle 2 Day 15, patients consented to the A171601-PP1 substudy will be asked to complete a Patient Pharmacokinetics Form (see Appendix IX) which will provide information about the previous 48-hours of palbociclib dosing (i.e. details on dose and time). After completion, the form should be collected, and the data should be reported in Rave on the Specimen Submission Form for A171601-PP1. Collect 1 x 5 mL of peripheral venous blood in a lavender top (EDTA) tube prior to the patient receiving the daily dosage of palbociclib on Cycle 1 Day 1 and Day 15, and Cycle 2 Day 15. Invert the tubes approximately 8-10 times to mix the EDTA, and then centrifuge at room temperature for 10 minutes at 1500g. Aliquots of plasma will then be placed in labelled polypropylene tubes (1 mL in each of two tubes) and stored at -70 to - 80 ºC until shipped on dry ice.

Label all plasma samples with the following identification information:

1) Date of Collection
2) Time of Collection (i.e. actual time the blood sample was obtained)
3) Alliance Patient ID Number
4) Patient Initials
5) Alliance Study Number (i.e. A171601-PP1)
6) Sample Type (e.g. Plasma)

If labels are used, please ensure labels are carefully attached to the tubes and are not likely to fall off when frozen or during shipping.

Ship specimens and copies of the completed Pharmacokinetics questionnaires to the Alliance Laboratory at the University of Pittsburgh (See Section 6.2.1) with Priority Overnight on Monday through Thursday for next day delivery. Do not ship specimens the day before a holiday. The University of Pittsburgh does not accept Saturday deliveries.

6.3 Digital Image Submission Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1 TRIAD Access Requirements

- A valid CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.2 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted]

6.3.3 Procedures for Data Submission via TRIAD

Collection of CT/PET-CT and Bone images is required. Images will be collected digitally for archival and retrospective purposes at the following time points:

- **Baseline** (within 28 days prior to patient registration)

- **Restaging (**Day 1 of Cycle 4 (±2weeks) then every 12 weeks until end of treatment**)**

The complete CT/PET-CT and Bone scan imaging data in digital **DICOM** format will be submitted **electronically** to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) **within no more than 3 business days** upon patient enrollment (at baseline) or upon the image acquisition completeness (at follow-ups). BMP files, JPG files, or hard copies (films) are not acceptable.

Imaging data should be submitted electronically to IROC Ohio via **TRIAD**. The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail [redacted] per the request by participating sites before their first data submission.

If TRIAD approach is not achievable at site, alternatively site needs to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., A171601), and use the following electronic approaches for data submission:

1) Web Transfer [redacted]

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail [redacted], per the request by participating sites before their first data submission.

2) FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail [redacted], per the request by participating sites before their first data submission.

Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution. Submit these data to:

[redacted]

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email [redacted] to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number

2) Scan time point (i.e., baseline)

3) Date of scans

4) Institution name

IROC Ohio will notify site within **2 business days** of the data receipt, and then, within **3 business days** following the data receipt, of the quality check report.

Any questions or problems about the data submission to IROC Ohio, call IROC Ohio at [redacted] for help

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin **within 14 days of registration**.

For questions regarding treatment, please see the protocol contacts on page 2.

It is acceptable for protocol treatment to be delivered within a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of protocol treatment delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

The study will be an open label, single arm, phase II safety and tolerability study of the combination of palbociclib and letrozole or fulvestrant in patients age 70 or over with hormone-receptor positive, HER2-negative metastatic breast cancer. All patients who begin study treatment will be included in the analysis of all clinical endpoints.

Agent	Starting Dose	Route of Administration	Frequency of Administration
Palbociclib	125 mg/day	Orally	Once daily on Days 1-21 of each 28-day cycle
Letrozole	2.5 mg	Orally	Once daily on Days 1-28 of each 28 day cycle

OR

Palbociclib	125 mg/day	Orally	Once daily on Days 1-21 of each 28-day cycle
Fulvestrant	500 mg	IM injection	Day 1 and Day 15 of Cycle 1, then Day 1 of every subsequent cycle

Treatment will continue until disease progression or unacceptable toxicity.

7.1 Palbociclib

A cycle will be four weeks (28 days) in duration. Treatment will be administered in an outpatient setting. Palbociclib will be administered per the following schedule:

1. 21 consecutive days of 125 mg palbociclib, taken orally with food and taken at approximately the same time each day.
2. Following the 21 consecutive days, there will be 7 days off treatment to comprise a complete cycle of 28 days.

If a patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Missed doses will not be made up and cycle length stays the same. Palbociclib capsules should be swallowed whole and should be taken in combination with endocrine therapy (if taking letrozole).

7.2 Letrozole

Letrozole will be prescribed and administered per MD discretion and dosing should follow the package insert guidelines. The recommended dose is 2.5 mg daily. Doses missed for toxicity will not be made up. Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability.

7.3 Fulvestrant

Fulvestrant will be prescribed and administered per MD discretion and dosing should follow the package insert guidelines. The recommended dose is 500 mg given IM on Days 1 and 15 of Cycle 1, and then given every 28 days. Doses missed for toxicity will not be made up. Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability.

7.4 Adherence, Geriatric Assessment, and Patient Perspective

Pill diaries will be collected at the end of cycles 1-3 of treatment to ascertain dose delivered adherence to palbociclib. Adherence to palbociclib will be measured by patient self-report in dedicated patient diaries at the end of the first 3 cycles.

A cancer specific **geriatric assessment** will be captured pre-treatment, after 3 cycles, and at the end of treatment. See Section 11.0.

To further assess the patient's perception of treatment efficacy of palbociclib in addition to endocrine therapy, we will ask our participants to complete the following questionnaires at the end of treatment: Was It Worth It (Appendix III) and Overall Treatment Utility (Appendix IV), the EQ-5D-3L (Appendix V) and PRO-CTCAE questionnaire (Appendix VI). These questionnaires will provide a better understanding of the patient's perspectives regarding the benefits and side effects of treatment, in combination with an assessment of treatment efficacy and toxicity. See Section 11.0.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should avoid immunizations with live virus vaccines.

8.1.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.4 Treatment with hormones for breast cancer treatment or other chemotherapeutic agents may not be administered.

8.1.5 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.6 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.7 Palliative radiation therapy may not be administered.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.8 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.

The use of colony stimulating factors, filgrastim (G-CSF), pegfilgrastim and sargramostim (GM-CSF) is discouraged but may be used in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per ASCO guidelines . Investigators should use their own discretion in using the CSFs in this setting which must be documented and reported on forms.[53]

8.1.9 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to (drug[s]) as per institutional standards.

8.1.10 CYP3A Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A is strongly discouraged while on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A and are not allowed during treatment with palbociclib.

- Indinavir
- Clarithromycin
- Ketoconazole
- Grapefruit juice

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.11 CYP3A Inducers

Chronic concomitant treatment with strong inducers of CYP3A is strongly discouraged while on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A and are not allowed during treatment with palbociclib.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.12 CYP2A6 Substrates

Chronic concomitant treatment with substrates of CYP2A6 is strongly discouraged while on this trial. The following drugs are EXAMPLES of CYP2A6 substrates and are not allowed during treatment with letrozole.

- Dexmedetomidine
- Tegafur

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP2A6. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.2 Dose Modifications

Palbociclib cycle length will remain 28 days (± 2 days) (despite a delay in initiating a new cycle of palbociclib); endocrine therapy may continue to be administered per the preplanned schedule.

- Dose holds/reductions of letrozole or fulvestrant will occur per the package insert and the treating investigator's discretion.
- Dose escalation will not be permitted in this study.
- Palbociclib doses missed for toxicity will not be made up.
- The initiation of a new cycle may be delayed for up to 7 days

CTEP – AERS reporting may be required for some adverse events. See Section 9.0. PRO-CTCAE data should not be used for dose modifications.

8.2.1 Dose Levels

Dose Level	Palbociclib Dose
Starting Dose	125 mg/day
-1	100 mg/day
-2	75 mg/day

8.2.2 Hematologic adverse events (except lymphopenia, unless associated with clinical events, e.g., opportunistic infections):

Monitor complete blood counts prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

For grade 3 events:

Day 1 of cycle:

Omit palbociclib, repeat complete blood count monitoring within 1 week. Upon recovery to Grade ≤2, start the next cycle at the same (previous) dose.

Day 15 of first 2 cycles:

- If Grade 3 on Day 15, continue palbociclib at current dose to complete cycle and repeat complete blood count on Day 22.
- If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.
- Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.

For grade 3 neutropenia with fever ≥38.5 °C and/or infection, and Grade 4 events:

- Omit palbociclib until recovery to Grade ≤2.
- Resume at the next lower dose.

8.2.3 Non Hematologic adverse events:

For all grade 3 and higher events related to palbociclib, omit palbociclib until recovery to Grade ≤ 1, or Grade ≤2 (if not considered a safety risk for the patient).

- Resume palbociclib at the next lower dose at the discretion of the treating physician.
- Permanently discontinuing palbociclib is recommended in patients experiencing severe Interstitial Lung Disease/pneumonitis.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

To complement CTCAE reporting, patients will self-report their side effects using the PRO-CTCAE. The specific PRO-CTCAE items for this protocol can be found in Appendix VI. PRO-CTCAE should not be used for determining attribution or reporting of serious adverse events.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Event Solicited form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

CTCAE v. 5.0 Term	PRO-CTCAE v. 1.0 Term	CTCAE v.5.0 System Organ Class (SOC)
Neutrophil count decreased		Investigations
Platelet count decreased		Investigations
White Blood cell count decreased		Investigations
Anemia		Blood and lymphatic system disorders
Febrile Neutropenia		Blood and lymphatic system disorders
Nausea	Nausea	Gastrointestinal Disorders
Anorexia	Decreased Appetite	Metabolism and Nutritional Disorders
Diarrhea	Diarrhea	Gastrointestinal disorders

Vomiting	Vomiting	Gastrointestinal disorders
Mucositis oral	Mouth/throat sores	Gastrointestinal disorders
Fatigue	Fatigue	General disorders
Peripheral Sensory Neuropathy	Numbness and Tingling	General disorders
Thromboembolic event		Vascular disorders
Upper Respiratory Infection		Infections and Infestations
Urinary Tract Infection		Infections and Infestations

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager. PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

- Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated		a	a	a	a
Unlikely		a	a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

- a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
- b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Alliance A171601 Reporting Requirements

Expedited reporting requirements for adverse events that occur on studies under an IND/IDE ≤ 30 Days of the last administration of the investigational agent/intervention [1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported in Rave.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected,

molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 fatigue and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 fatigue does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 diarrhea does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 diarrhea and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 neutropenic fever and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- CTEP-AERS reports should be submitted electronically.

9.4 CAEPR

Revised Palbociclib CAEPR – Version 2.4, September 13, 2019

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Palbociclib (PD-0332991, NSC 772256)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification.

Frequency is provided based on 1751 patients. Below is the CAEPR for Palbociclib (PD-0332991).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, September 13, 2019[1]

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
EYE DISORDERS			
	Blurred vision		
	Dry eye		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Skin and subcutaneous tissue disorders - Other (rash)[4]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fulvestrant.

[4]Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, and dermatitis.

[5]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on palbociclib (PD-0332991) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that palbociclib (PD-0332991) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (paroxysmal atrial fibrillation with rapid ventricular response); Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EYE DISORDERS - Cataract; Eye disorders - Other (retinal hemorrhage)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Myalgia; Neck pain; Osteonecrosis; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysphasia; Intracranial hemorrhage; Nervous system disorders - Other (peripheral neuropathy)[5]; Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Psychiatric disorders - Other (altered mental status)
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Oropharyngeal pain; Pleural effusion; Postnasal drip; Pulmonary edema; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Palbociclib (PD-0332991) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 General Considerations:

All study agents are to be administered at the registering institution.

10.2 Palbociclib

IND Exempt: Palbociclib is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for Palbociclib; this investigation will use an approved route of administration and dosage of Palbociclib and has no factors that increase the risk of the product; this investigation will be in compliance with 21CFR parts 56, 50, and 312.7; and neither the investigator nor sponsor will promote or represent that Palbociclib is safe or effective for the context that is under investigation in this study.

Procurement

Palbociclib is a commercially available agent and filled with prescription.

Formulation

Palbociclib is supplied as a 125 mg, 100 mg, or 75 mg tablet. Palbociclib is a yellow to orange powder and the 125mg capsule is an opaque hard gelatin, size 0 capsules with a caramel cap and body, printed with white ink "Pfizer" on the cap, and "PBC 125" on the body. The 100 mg capsules are opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink "Pfizer" on the cap and "PBC 100" on the body. The 75 mg capsules are opaque hard gelatin capsules, size 2, with light orange cap and body, printed with white ink "Pfizer" on the cap and "PBC 75" on the body.

Inactive ingredients present in the capsule include: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells

The light orange, light orange/caramel and caramel opaque capsule shells contain gelatin, red iron oxide, yellow iron oxide, and titanium dioxide; and the printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone

Storage and Stability

The intact bottles should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15 to 30°C (59 to 86°F)

Administration

Dose: 125mg of palbociclib administered orally once a day around the same time every day for 21 consecutive days followed by 7 days off to comprise a cycle of 28 days.

Route of Administration: Orally with meals and patients should be encouraged to take their dose at approximately the same time each day. If a patient vomits or misses a dose, an additional dose should not be taken that day. Instead the next prescribed dose should be taken at the usual time. Palbociclib capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Patients should avoid consumption of grapefruit or grapefruit juice.

Drug Interactions

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. Palbociclib interacts with CYP3A inhibitors and CYP3A inducers. Avoid concurrent use of palbociclib with strong CYP3A inhibitors or inducers.

Adverse Events

The following are common (≥ 10%) adverse events occurring in at least one patient who received palbociclib plus letrozole in clinical trials.

Infections and Infestations: Upper Respiratory Infection

Blood and Lymphatic System Disorders: Neutropenia, Leukopenia, Anemia, Thrombocytopenia

Metabolism and Nutrition Disorders: Decreased Appetite

Nervous System Disorders: Peripheral Neuropathy

Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis

Gastrointestinal Disorders: Stomatitis, Nausea, Diarrhea, Vomiting

Skin and Subcutaneous Tissue Disorders: Alopecia

General Disorders and Administration Site Conditions: Fatigue, Asthenia

Nursing Guidelines

1. Agent should be administered with food. Do not crush, break or open capsules prior to administration.
2. Monitor CBC w/diff as cytopenias are common and require dose reductions. Instruct patients to report signs or symptoms of infection and/or any unusual bruising or bleeding to the study team.
3. GI symptoms are common, including nausea/vomiting, stomatitis and diarrhea. Treat symptomatically and monitor for effectiveness. Some side effects may require dose reductions.
4. Patients should avoid grapefruit and grapefruit juice, due to possible increase in the serum concentration of palbociclib.
5. There are drug to drug interactions with CYP3A4 substrates. Obtain a complete list of patient medications including OTC and herbal products. Instruct patients to report any new mediations to the study team immediately.
6. Warn patient of risk of thromboembolic events, specifically pulmonary embolism.
7. Warn patients of possibility of alopecia.
8. Patients may experience upper respiratory infection. Instruct patients to report URI symptoms to study team.
9. Rarely patients may experience peripheral neuropathy. Monitor patients closely who may have preexisting CIPN from previous therapy.

10.3 Fulvestrant

Please refer to the FDA-approved package insert for fulvestrant for product information, extensive preparation instructions and a comprehensive list of adverse events.

Other names: Faslodex

Classification: Estrogen receptor antagonist

Molecular Formula: $C_{32}H_{47}F_5O_3S$ M.W.: 606.77

Approximate Solubility: Each injection contains as inactive ingredients alcohol, USP, benzyl alcohol, NF, and benzyl benzoate, USP as co-solvents and castor oil, USP as a co-solvent and release rate modifier.

The solution is a clear, colorless to yellow, viscous liquid.

Procurement

Fulvestrant is a commercially available agent and filled with prescription.

Storage:

The syringes of fulvestrant for all cycles of treatment should be stored in the original container and refrigerated at 2°- 8°C (36°- 46°F).

Administration:

Routes of Administration: IM Injection

Method of Administration: Remove glass syringe barrel from tray and check that it is not damaged. Peel open the safety needle (SafetyGlide™) outer packaging. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap. Twist to lock the needle to the luer connector. Remove needle sheath. Remove excess air from the syringe (a small gas bubble may remain).

For this study, fulvestrant will be administered at a dose of 500 mg (2 X 250 mg injections) IM or as indicated per the package insert on Day 1 and Day 15 of Cycle 1 and then on Day 1 of each cycle in each subsequent cycle. Administer intramuscularly slowly in the buttock. (NOTE: 500 mg dose will require one 250 mg injection in each buttock.) Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered. Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps container.

Toxicity:

The most common toxicities reported in trials of fulvestrant to date include gastrointestinal symptoms, menopausal symptoms and injection site reactions. Nausea and vomiting have been the primary GI symptoms, occurring in approximately 50% of patients in phase III trials. They were generally of mild to moderate severity. Hot flashes were reported in approximately 20% of patients. Injection site reactions include pain, hemorrhage and inflammation. Such reactions may be more frequent when fulvestrant is administered as 2 injections of 2.5 ml (125 mg) each, as compared with 1 injection of 5 ml (250 mg).

Potential Drug Interactions: In *in vitro* studies using human hepatocytes, fulvestrant was metabolized predominantly by conjugation. The metabolites thus formed are thought to possess no estrogenic activity and minimal anti-estrogenic activity. In studies using human liver microsomes, fulvestrant inhibited the activity of CYP1A2, 2C9 and 3A4 minimally. CYP3A4 did metabolize fulvestrant in these studies, but the human hepatocyte studies noted above indicate conjugation is a more important metabolic pathway. In addition, studies in healthy volunteers indicate that fulvestrant metabolism is not significantly affected by inducers or inhibitors of CYP3A4, nor does fulvestrant affect the metabolism of 3A4 substrates. Thus, fulvestrant is not expected to be involved in significant drug interactions mediated by CYP3A4.

Nursing guidelines

1 Rarely a blood-tinged vaginal discharge has been reported infrequently during therapy. Advise patients that this is a possibility and that studies have shown no effects on vagina or endometrium.

2 Monitor LFT's based on protocol requirements. Report increased LFT's to treating physician.

3 Hot packing the injection site for a short while after injection may prevent the possible bruising, tenderness, and/or erythema at the IM injection site.

4 Instruct patient to report any signs or symptoms of blood clots. Patients with calf tenderness or burning, and/or chest pain (pulmonary embolus) should be evaluated by a physician immediately.

5 Warn patient of possible hot flashes. Assess severity and discuss non-hormonal treatments with treating physician. Assess treatment for efficacy.

6 May cause mild GI symptoms (nausea, anorexia, vomiting, constipation). Treat symptomatically and monitor for effectiveness of intervention.

10.4 Letrozole

Please refer to the FDA-approved package insert for letrozole for product information, and a comprehensive list of adverse events.

Other name: Femara®

Classification: Aromatase inhibitor

Molecular formula: $C_{17}H_{11}N_5$

Procurement

Letrozole is commercially available and filled with prescription.

Formulation:

Letrozole is supplied as 2.5 mg, dark yellow, film-coated tablets in bottles of 30 tablets.

Storage and Stability

Intact bottles of letrozole should be stored at 25°C (77°F), excursions permitted to 15 to 30°C (59 to 86°F)

Administration

Letrozole will be taken orally, at a dose of 2.5 mg once daily without regard to meals.

Toxicities

The most common adverse events reported include arthralgia, flushing, asthenia, edema, headache, dizziness, hypercholesterolemia, bone pain. Of concern, primarily with long-term use of aromatase inhibitors including letrozole, are effects on lipid metabolism with subsequent cardiovascular events and on bone resorption. Other less frequent adverse events include bone and muscle pain.

Nursing guidelines

1 Manage hot flashes with non-hormonal interventions (ie: venlafaxine XR 75 mg daily).

2 Manage pain (arthralgias). Instruct patient to report unrelieved pain.

3 May take with food if needed for nausea. Instruct patient to report unrelieved nausea or vomiting.

4 Assess for changes in bowel patterns. Manage diarrhea or constipation with non-prescription drugs. Tell patients to report unrelieved diarrhea or constipation.

5 If patient experiences difficulty breathing or sudden onset chest pain, instruct them to seek emergency medical attention immediately.

6 Monitor for signs of edema, instruct patient to report any swelling in legs, feet, or hands.

11.0 MEASUREMENT OF EFFECT

11.1 Patient reported outcome measures

11.1.1 Geriatric assessment

A cancer-specific comprehensive geriatric assessment will be given at baseline, the first restaging (i.e., after 3 cycles of treatment and prior to cycle 4), and at the end of treatment (see Appendix II for Geriatric Assessment Survey). The cancer-specific comprehensive geriatric assessment includes an evaluation of functional status, co-morbidity, cognition, psychological status, social functioning and support, and nutritional status.[3] This assessment has been piloted in the Alliance (in legacy Cancer and Leukemia Group B [CALGB]). CALGB 360401 evaluated the feasibility of incorporating the Geriatric Assessment Tool into oncology cooperative group trials.[52] Patients were eligible to participate if they were age $\geq$ 65 and had signed consent for a cooperative group treatment trial. The Geriatric Assessment Tool was completed prior to initiation of the protocol-specified treatment. Ninety-three patients enrolled in this study. The median time to complete the assessment was 22 minutes, 88% of patients completed the patient portion without assistance, 88% satisfied with the assessment length, 98% reported there were no upsetting items, and 95% said the assessment was easy to comprehend. The Geriatric Assessment Tool met the protocol specified feasibility criteria for incorporation in oncology cooperative group trials.[52]

Several studies are emerging regarding the benefits of performing a comprehensive geriatric assessment for older patients with cancer. Factors evaluated in a comprehensive geriatric assessment can predict survival, predict toxicity to chemotherapy, and uncover problems not detected by a routine history and physical in initial consultation and follow-up care.[53, 54, 55] Consensus guidelines recognize the benefits and recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient.[56]

11.1.2 Overall treatment utility

We will be including a measure of Overall Treatment Utility (OTU) to assess the "objective and subjective measures of tolerability and acceptability". This is accomplished with an analysis of clinical benefits in conjunction with an analysis of whether toxicity and serious adverse events affect one's daily functions. This provides a way to quantify advantages and disadvantages from receiving treatment in this study, as well as an understanding of how patients may respond to treatment. OTU is useful in answering the following hypothetical question from the patient's perspective: "With the benefit of hindsight, are you glad you received treatment?" By including the OTU in this study, researchers and oncologists will be able to better understand the patient's perspectives regarding the benefits and side effects of treatment, in combination with an assessment of treatment efficacy and toxicity.

OTU is a novel composite endpoint developed by investigators of the FOCUS2 trial to assess the outcome of palliative chemotherapy[57]. The interpretation of clinical trials, especially in the palliative setting, often requires subjective synthesis of object data. Measures of efficacy are weighted against the toxic effects, convenience, and other variables before deciding which treatment is best. OTU helps integrate these measures into a single

composite endpoint. OTU combines clinical efficacy ("Is my patient alive without disease progression?"), clinical tolerability ("Did we avoid causing major harm"), and patient opinion ("Was my treatment worthwhile and acceptable?"). In the original study using OTU, the composite endpoint was found to be particularly useful when conventional outcomes were divergent (Oxaliplatin improved response rates and progression free survival, yet resulted in increased toxicity), and helped confirm the benefit of Oxaliplatin[57]. We will measure OTU by assessing clinical benefit and tolerability/acceptability at the end of treatment. (See Study calendar Section 5.0 and Appendix IV). OTU is scored as **Good OTU** (clinical or radiographic evidence or disease progression, no major negative treatment effects in terms of toxicity or patient acceptability), **Intermediate OTU** (either clinical deterioration but no negative treatment effect, or a significant negative treatment effect but no clinical deterioration), or **Poor OTU** (both clinical deterioration and a major negative treatment effect, or death).

11.1.3 Was it worth it questionnaire

The Was It Worth It instrument (Appendix III) was developed to learn more about the experience of patients participating in clinical trials. It is comprised of four brief questions, and it has also been called the "Trial Satisfaction" survey.[58] Although formal validity and reliability data for this instrument are not yet available, multiple cooperative group studies have used it to measure how satisfied patients end up with their decision to enroll on a clinical trial.[59-63]

11.1.4. Quality of life

All participants-will be asked to fill out a short QOL survey and on paper at each provider assessment visit at baseline through the start of cycle 6 (unless patients come off study treatment before that time). Appendix V has the required EQ-5D-3L survey.)

11.1.5 Adherence evaluation

Pill diaries will be collected at the end of each cycle of treatment to ascertain dose delivered adherence to palbociclib for a maximum of three cycles from initiation of protocol treatment. Adherence to palbociclib will be measured by patient self-report in dedicated patient diaries. (Appendix VII). Patients will be asked to bring their pill diaries to every clinic visit.

11.2 Measurement of tumor response and schedule of evaluations

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).

Per the new RECIST criteria, as disease response is not the primary endpoint of this trial, confirmatory scans following documentation of progression or response will not be required. Rather, progression/response will be determined based on results of the single scan.

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.[64]

Schedule of Evaluations

For the purposes of this study, patients should be reevaluated for tumor response every 12 weeks.

While on study, a CT of the chest, abdomen, with or without pelvis (or PET-CT as above) will be performed every 12 weeks (±2 weeks). A bone scan will be done at restaging time points if clinically indicated (or to confirm a complete response).

Toxicity Evaluation

Toxicity evaluations will be performed Days 1 (±2 days), 8 (±2 days), and 15 (±2 days) of Cycles 1 and 2. For subsequent cycles, toxicity evaluations will be done on Day 1 (±2 days). Additional adverse events captured in-between will also be recorded. (Please see study calendar Section 5.0)

All toxicity related dose interruptions or reductions, hospitalizations, and adverse events will be noted. Patients will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade >2 toxicities. Any toxicities will be recorded in the patient's medical record and highest grade of that toxicity will be reported on the case report forms.

11.3 Definitions of Measurable and Non-Measurable Disease

11.3.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10mm with conventional techniques (CT, or caliper measurement). Lymph nodes greater than 15mm on short axis are considered measurable as well. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Tumor lesions in a previously irradiated area are not considered measurable disease.

11.3.2 Non-Measurable Disease

All other lesions (or sites of disease), are considered non-measurable disease. Organomegaly, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT are all non-measurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Lymph nodes less than 15mm in the short axis cannot be used as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.4 Guidelines for Evaluation of Measurable Disease

11.4.1 Measurement Methods

All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.4.2 Acceptable Modalities for Measurable Disease

- **Conventional CT:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- **PET-CT:** If the site's protocol is to use a PET-CT, then a PET-CT with or without IV and oral contrast, can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.4.3 Measurement at Follow-up Evaluation:

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.5 Measurement of Treatment/Intervention Effect

11.5.1 Target Lesions & Target Lymph Nodes

Measurable lesions (as defined in Section 11.3.1) up to a maximum of 5 lesions in total, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.3.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 3 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.5.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.3.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.5.3.

11.5.3 Response Criteria

All target lesions and target lymph nodes followed by CT/PET-CT/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.2. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
  - Disappearance of all target lesions.
  - Each target lymph node must have reduction in short axis to < 1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.5.1).
- Progression (PD): At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.5.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  - See Section 11.4.2 for details in regards to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
  - Disappearance of all non-target lesions.
  - Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes
- Progression (PD): At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion

and target lymph node status. It must be representative of overall disease status change.)

- See Section 11.4.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.5.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.5.3

For Patients with Non-Measurable Disease Only

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* See Section 11.5.3

11.5.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.6 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 End of Treatment/Intervention

12.1 Duration of Treatment

Patients should continue protocol treatment until disease progression or unacceptable toxicity. There are no minimum required cycles of therapy.

12.2 Follow-up for patients who discontinue protocol therapy

12.2.1 Disease Progression

Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival every year per the study calendar (Section 5.0).

12.2.2 Unacceptable toxicity

Patients who discontinue treatment for unacceptable toxicities should continue to be followed for progression. Following progression, patients will be followed every year for survival.

In addition, patients who discontinue therapy within 1 year after registration will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade >2 toxicities. Resolution or stabilization of the adverse event will be recorded even if disease progression has occurred.

12.2.3 Other reasons for discontinuation of protocol therapy

Patients who discontinue treatment for any other reason than progression or unacceptable toxicity should continue to be followed for progression. Following progression, patients will be followed every year for survival. The reason for discontinuation of protocol treatment must be documented on the "Off treatment" form.

12.2.4 Discontinuation of Geriatric Assessment and Specimen Submission

Geriatric Assessment: Patients will complete the geriatric assessment at the end of treatment. If end of treatment occurs prior to the end of Cycle 3, the end of cycle 3 assessment need not be submitted. (That is, patients who discontinue protocol treatment prior to the end of cycle 3 will have completed a geriatric assessment at baseline and at the end of treatment.)

Specimen Submission: Patients who discontinue protocol treatment prior to the end of Cycle 3 must still be asked to submit an end of treatment blood sample rather than the prior to Cycle 4 blood sample listed in Section 6.2.

12.3 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoints:

The primary endpoint is the adverse event rate at 6 months, defined as the proportion of patients with documentation of grade 3 - 5 toxicity (regardless of attribution using the NCI CTCAE v.5.0 criteria).

13.2 Primary Endpoint Analysis:

A 95% binomial confidence interval for single proportions will be constructed for the severe toxicity rate occurring the first 6 months of treatment. Univariate relationships between the primary endpoint and various pre-treatment patient characteristics such as anemia, self-assessed functional status, or social support will be described via cross-tabulation and Fisher's exact testing. Exploratory logistic regression modeling, with limited generalizability due to the modest sample size, will be used to assess the relative contributions of these variables impact the likelihood of developing a severe toxicity during treatment. The strength of this association will be expressed in terms of an odds ratio and its associated 95% confidence interval. As a secondary analysis for this endpoint, we will also look at grade 3-5 toxicities occurring within the first 6 months of treatment that are at least possibly related to palbociclib. This analysis will be conducted in a similar fashion as the primary endpoint. To explore the relationship between the severe toxicity rate occurring within the first 6 months of treatment in this population and the type of endocrine therapy used (letrozole vs. fulvestrant), we will conduct a chi-square test or Fisher's exact test as appropriate.

13.3 Secondary Endpoints:

- All toxicities associated with the combinations as measured by NCI CTCAE v.5.0
- Dose reductions, dose holds, and hospitalizations
- Time to treatment failure (and reason for coming off study – toxicity, patient preference, progression)
- The percentage of doses of palbociclib taken each cycle for the first 3 cycles
- Results of the geriatric assessment, Was It Worth It (WIWI) Questionnaire, and Overall Treatment Utility (OTU)

13.4 Secondary Endpoint Analyses

13.4.1 Palbociclib Tolerability

Conclusions concerning the tolerability of this regimen in elderly patients will take into account the percentage of patients who develop grade 2 and higher toxicities including febrile neutropenia, leukopenia, thrombocytopenia, and anemia, GI side effects (nausea, diarrhea, decreased appetite, vomiting, stomatitis), fatigue, neuropathy, and thromboembolism , the percentage of patients who require dose modifications and the percentage of patients who refuse to continue on study treatment for any reason.

13.4.2 Reasons for Dose Reduction, Dose Holds, and Hospitalizations

Summaries of reasons for dose reductions, dose holds, and hospitalizations will be prepared. Any dose reduction will be considered and reason for dose reduction will be noted. Since palbociclib is given in combination with endocrine therapy as per standard of care, we are evaluating clinical endpoints based on tolerability of the combination. In the case report forms, we will capture whether the toxicity is due to the endocrine therapy or the palbociclib.

13.4.3 Time to Treatment Failure

Distributions time to treatment failure will be estimated using Kaplan-Meier methodology. Treatment failure is defined as a severe adverse event, disease progression or patient refusal to continue assigned treatment. We would include any reason that treatment is discontinued to time to treatment failure and not censor patients. The reason for treatment discontinuation will be captured.

13.4.4 Adherence to Palbociclib

Patients to be included in the analysis cohort will be those patients who have taken one or more doses of the study treatment. Those patients will be considered adherent to study treatment. For each of the first 3 cycles, an estimate of the proportion of patients who meet the criteria for adherence and its corresponding 95% confidence interval will be determined.

13.4.5 Response Rate as Determined by RECIST

The response rate is defined as the proportion of patients whose disease status met RECIST criteria for complete response (CR) or partial response (PR) on 2 consecutive evaluations at least 8 weeks apart. A 95% binomial confidence interval for the response rate will be constructed.

13.4.6 Progression Free Survival (PFS) and Overall Survival (OS)

Distributions of PFS and OS times will be estimated using Kaplan-Meier methodology. Progression free survival is defined as follows: "the time from start of treatment to the first of the following disease events: local/regional/distant recurrence, invasive contralateral breast disease, second primary or death due to any cause".

13.4.7 Geriatric Assessment, WIWI Questionnaire, and OTU

Descriptive statistics will be provided for responses from the WIWI Questionnaire and the OTU. General linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment that may be predictive of toxicity/dose reduction, dose holds, or hospitalizations. Repeated measures models and graphical methods will also be utilized in an exploratory fashion to assess the impact of the length of treatment on the results of the geriatric assessment.

13.4.8 Sarcopenia analysis

Abdominal or thoracic CT images performed as part of routine care for staging and disease monitoring during the trial, (which is every 12 weeks -See Study calendar Section 5.0) will be acquired from study sites. Using the transverse section at the L3 level for abdominal imaging (as most highly correlated with total body muscle mass [r2= 0.86][65]) or at L1 level for thoracic imaging (as most highly correlated with L3),[66] skeletal muscle area (SMA) will be quantified within a Hounsfield unit (HU) range of -29 to +150 HU using Slice-O-Matic software (v.4.3;Tomovision, Montreal, Quebec, Canada). A Skeletal Muscle Index (SMI) will then be calculated using the following formula: SMI = SMA (cm2) / patient height (m2). Estimated LBM will also be calculated using the following formula: [LBM (kg) = 0.30 × [SMA (cm2)] + 6.06].15 Mean skeletal muscle density (SMD) will be derived by averaging HU of skeletal muscle. Skeletal muscle gauge (SMG) will then be calculated by multiplying SMI x SMD. Subcutaneous adipose tissue (SAT) area will also be calculated from extra-muscular tissue with density between −190 and -30 HU, and visceral adipose tissue (VAT) from non-subcutaneous tissue with density between -150 and -50 HU. The primary measure of skeletal muscle mass will be SMI, and other measures will be assessed secondarily.

Descriptive statistics will be provided for body composition variables including SMI, SMD, SMG, and LBM. Sarcopenia will be treated as a binary variable (based on cut-points of SMI from prior literature ; SMI <41cm2/m2 = sarcopenic [70]) and differences in grades [67-69] chemotherapy toxicity and adverse events will be analyzed using two group t-tests and Fisher's exact test. Depending on the number of abdominal versus thoracic scans that are utilized, analyses may be stratified by location of SMA measurement (L3 versus L1). Relative risks (RR) and 95% Confidence Interval (CI) will be reported for associations between sarcopenia and grade 3-5 toxicity and hospitalization, and secondarily for SMD and SMG (based on literature based cut-points).[70,71] Both unadjusted and adjusted RR will be calculated using Poisson regression models with robust variance.[72] Covariates in the model include age, and race/ethnicity. Receiver operating characteristic (ROC) curves will be generated, as well as the area under the curve (AUC), to evaluate the predictive ability of each body composition measure with grades 3-5 toxicity. Depending on the availability of subsequent follow up imaging after 3 treatment cycles, we will describe changes in body composition from baseline to start of cycle 4. We will examine variables associated with skeletal muscle loss during treatment and whether skeletal muscle loss during treatment is associated with the presence of grade 3-5 toxicity and adverse events.

13.4.9 EuroQol 5D 3L questionnaire:

The EQ-5D-3L will be scored and the results will be evaluated descriptively and graphically.

13.4.10 PRO-CTCAE:

We will evaluate feasibility of PRO-CTCAE reporting in this population by looking at the compliance rates of the PRO-CTCAE. The PRO-CTCAE will be considered feasible if 75% of the patients completed 75% of the PRO-CTCAE questionnaires. We will also compare symptoms reported by patients on their PRO-CTAE inputs compared to what is reported in clinic using traditional AE evaluations. PRO-CTCAE results will be summarized and presented descriptively.

13.5 Sample Size

The sample size was determined based on Turner et al.'s finding that the severe toxicity rate in patients age 29 – 88 (approximately 25% age ≥ 70) was 70%.[2] The sample size is 88 patients which will take into account potential dropout which will allow for 80 evaluable patients. Given a sample of 80 patients, the widest half-width of the 95% confidence limits for the rate of severe toxicities will be less than or equal to 0.1. Assuming a rate of severe toxicities of 70%, our 95% confidence interval will range from 0.6 to 0.8.

Additionally, to ensure we have sufficient patients who are aged 75+ to estimate the severe toxicity rate and safety of palbociclib, we will accrue patients until we have 40 patients who are 75 or older. Given a sample of 40 patients, the widest half-width of the 95% confidence limits for the rate of severe toxicities will be less than or equal to 0.142. Assuming a rate of severe toxicities of 70%, our 95% confidence interval will range from 0.558 to 0.842.

13.6 Interim analysis and stopping rules:

After approximately 20 patients have completed one full cycle, the study team will review the data (including the toxicity profile, rates of dose reduction, holds and hospitalizations) and assess if the dose being studied is too high, that is if more than 50% of patients experience a dose reduction. If so, a reduction of the dose will be considered, otherwise the study will continue to completion at the planned dose.

Per correspondence with NCI, we include a separate stopping rule for patients with a performance status of 3 or 4 to modify eligibility criteria if there is evidence that patients with PS 3 or 4 do not seem to tolerate the regimen. If, in the review described above of the first 20 patients, more than 50% of the patients with performance status 3 or 4 experience an adverse event, we will consider changing the eligibility requirements to preclude patients with PS 3or 4 from participating in the study.

With Update 2 to the study, we have revised eligibility criteria to restrict study participation to patients with ECOG performance status 0-2. (See Section 3.2.11)

13.7 Study Reporting

This study will be monitored by the study team (including the Study Chair, Committee Chair, study statisticians, protocol coordinator, and Alliance Executive Officer) on a monthly basis, to assess severe adverse events. Reports containing a summary of adverse events will be reviewed on these calls. The study team will also monitor the accrual rate.

13.8 Inclusion of Women and Minorities

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	0	1	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	0	2	0	5
White	70	0	10	0	80
More Than One Race	0	0	0	0	0
Total	75	0	13	0	88

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 EXPLORATORY CORRELATIVE AND COMPANION STUDIES

There will be 3 sub studies and all patients are encouraged to participate.

14.1 Correlative Science: Circulating markers of inflammation as potential markers predictive of toxicity among elderly patients enrolled to Alliance A171601 (Alliance A171601-ST1)

Alliance A171601-ST1 will evaluate circulating markers of inflammation as potential markers predictive of toxicity among older patients with Estrogen receptor positive, HER2 negative metastatic breast cancer.

14.1.1 Background

There is great heterogeneity in the ability of older adults to tolerate cancer treatment. Some older patients tolerate treatment well and derive as much benefit from treatment as younger patients, while others have increased rates of toxicity resulting in treatment reductions and/or cessation of treatment. The best-studied tools to predict toxicity are comprehensive geriatric assessments, which require time and resources that limit their use in routine oncology practice. A measure of circulating biomarkers to predict toxicity would be an extremely valuable tool to complement the cancer-specific geriatric assessment to guide the clinician in making treatment decisions and avoid excessive toxicity in this population. This proposal aims to evaluate circulating markers of inflammation as potential markers predictive of toxicity among older women with metastatic breast cancer. This class of markers was chosen based on their correlation with physical function, functional decline, and mortality in the general geriatric population, as well as emerging evidence of their secretion by senescent cells associated with the aging process. In addition to toxicity, this study will also assess for a correlation between baseline markers of chronic inflammation and other important outcomes such as functional decline, and treatment modification.

Levels of circulating pro-inflammatory mediators such as IL-6 and TNF-alpha, D-dimer, and plasminogen activator inhibitor (PAI)-1, increase with age.[73-75] These markers are proposed to accelerate the aging process and exacerbate multiple age-related diseases.[76-78] There is a co-stimulatory affect between markers of inflammation and pro-thrombotic factors. Cytokines such as TNF-α and IL-6 stimulate production of pro-thrombotic factors such as PAI-1 and fibrinogen.[79] In turn, D-dimer, a marker of the clotting process, has been shown to induce synthesis and release of cytokines IL-1B, IL-6, and PAI-1.[80] Likewise, when vascular cell adhesion molecule (VCAM) is exposed to inflammatory markers TNF-α and IL-1B, it is cleaved to soluble (s)-VCAM, which is elevated in patients with age-related diseases.[81] Thus, we refer to markers of inflammation and coagulation discussed in this proposal collectively as 'inflammatory mediators'.

Several studies have shown that inflammatory mediators correlate with measures of physical function, and are elevated to a greater degree in frail patients than in age-matched, non-frail controls.[10-16] A study of 110 patients > 75 years demonstrated that a combination of inflammatory markers (TNF-α, IL-6, CRP) and low albumin correlated with lower physical function scores, independent of age, sex, body mass index (BMI), smoking status, number of co-morbidities and number of medications[82]

In the general geriatric population, elevated chronic inflammatory and pro-coagulant markers predict functional decline.[83-90] An analysis of disabled women ≥ 65 years showed higher IL-6 levels at baseline were associated with higher levels of functional decline including decreased mobility, activities of daily living deficits, increased walking limitations and decreased walking speed, compared to women with low IL-6 levels.[87] These

markers also correlate with functional decline after hospitalization and postoperative complications from oncologic surgery.[85,91]

Markers of chronic inflammation and coagulation are also associated with all-cause mortality risk in the elderly[83,84,88,90] In a population of community dwelling adults (mean age 78), soluble (s)-VCAM was independently correlated with poorer functional status at baseline (HR 1.2, p = 0.002).[88] After adjusting for functional status, demographic factors and comorbidities, higher plasma s-VCAM, D-dimer, and IL-6 concentrations were independently related to mortality within 4 years. Inflammatory mediators can have greater predictive ability among patients without baseline functional impairments, suggesting they may identify pre-frail patients that may not otherwise have been identified without extensive geriatric assessment testing[83, 90, and 92]

Previous studies have demonstrated the utility of inflammatory marker measurement in cancer patients. In a study evaluating gait speed of 329 older participants within two physical activity intervention studies, those with an increasing number of elevated inflammatory markers (IL-6, TNFR2, and D-dimer) had lower gait speeds (linear trend p<0.0001; Table 1). This effect was more pronounced among the 6% of patients that were cancer survivors (linear trend p=0.009). The patients with a cancer diagnosis and two elevated biomarkers had a gait speed of 0.88 meters/second (+/-0.37), which is well below the normal gait speed of 1.0 m/sec. The group of cancer survivors also had a clinically meaningful slower gait speed compared to the group without a cancer diagnosis and three elevated biomarkers (-0.20 m/sec). This study indicates circulating markers of inflammation can identify cancer patients in need of targeted interventions to prevent further functional decline.[93]

Investigators outside of the United States have recognized that systemic inflammation plays a major role in the decline of cancer patients, especially in terms of nutrition and physical function. The systemic inflammation-based Glasgow Prognostic Score (GPS), based on levels of C-reactive protein (CRP) and hypoalbuminemia, was derived as a surrogate of systemic inflammatory status. Data from 8,333 patients from 28 studies in patients with operable cancer demonstrate the GPS was an independent predictor of survival (HR range 1.5 – 5.1).[94] Fourteen of these studies involved patients with colorectal cancer and the prognostic significance of the GPS was independent of stage, pathological features, and comorbidity. Similar prognostic ability of the GPS was seen in 11 studies involving 1,504 patients with metastatic cancer. In a study of 56 patients with advanced-stage colorectal cancer, the GPS not only predicted survival, but it also predicted toxicity to chemotherapy[95] A higher GPS score correlated with higher grade 2/3 diarrhea and higher incidence of grade 2/3 toxicity compared to those with lower scores (p = 0.023 and 0.015 respectively). Other cytokines including IL-1β, IL-6, IL-2, IL-12, IL-8, TNF-α, MIP-1α, and MIP-1β correlated with clinical outcomes.

Emerging data suggest cellular senescence is an underlying process contributing to the increase in circulating inflammatory and pro-thrombotic factors associated with functional decline and mortality in the elderly.[18,29] Senescent cells accumulate with age as a reaction to life-long cellular stress. Although senescent cells are not mitotically active, they acquire a senescence-associated secretory phenotype (SASP), with increased production of proteins involved in chronic inflammation and coagulation, very similar to the markers associated with poorer physical function and mortality in the elderly.[96-97] Therefore, this proposal includes some markers of chronic inflammation that are part of the SASP to evaluate if they are elevated in patients who experienced adverse outcomes with cancer treatment.

Although chronic inflammatory mediators have not been established as true aging biomarkers, the fact that they correlate with measures of physical status, functional decline, and mortality in the older adult population suggests they may reflect underlying biologic processes that could predict a patient's risk of toxicity from cancer treatment and therefore, their ability to tolerate it. The levels of inflammatory mediators can be measured with ELISA assays on plasma samples collected during blood draws routinely done for cancer management. Therefore, the measurement of these levels could become an efficient way of providing the oncologist insight into potential tolerance of cancer therapy and provide guidance as to the most appropriate regimens and doses to prevent excessive toxicity for the older patient.

14.1.2 Objectives

- To explore the association between baseline chronic inflammatory mediator levels and development of adverse events.
- To explore the association between baseline chronic inflammatory mediator levels and treatment modification.
- To explore the association between baseline chronic inflammatory mediator levels and baseline physical function as assessed by the cancer-specific geriatric assessment.
- To explore the association between baseline chronic inflammatory mediator levels and decline in physical function as assessed by the cancer-specific geriatric assessment.

14.1.3 Methods

V-Plex panels are 10-spot 96-well plates. Individual panels measure 10 cytokines important in inflammatory responses and immune system regulation, and we anticipate running three V-plex panels for a total of 30 analytes tested. These 10-spot assays can detect secreted biomarkers and assess cytokines important in characterizing TH1 and TH2 subsets of T cells important in several inflammatory disorders. We will also run non 10-spot panels for TNFR-1, TNFR-2, and D-dimer.

The MesoScale Discovery (MSD) platform will be utilized for testing (Meso Scale Discovery Rockville, Maryland). Our proposed studies require 100uL of sample per 10 analytes tested on the V-Plex 10-spot platform. Since we plan to use 3 separate V-Plex panels, we anticipate using approximately 300 uL of sample to characterize expression of 30 cytokines. Additional markers being tested in separate kits include TNFR-1 and TNFR-2, as well as D-dimer, which will add another 200 uL of sample requirement. Therefore, the total minimum sample requirement is 500 uL of plasma. Additional sample would be favored, since at least 20% additional sample may be required for error and or pipetting losses. The V-Plex kits are designed for the analysis of all or any combination of these cytokine biomarkers in cell culture supernatants, serum, plasma, and urine.

Plasma samples are required for all testing, which will be run in duplicate using the following kits:

KIT#1: **IFN-gamma, IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-alpha**
Level of detection: IFN-γ: 0.04 pg/mL IL-2: 0.22 pg/mL IL-4: 0.14 pg/mL IL-5: 0.07 pg/mL IL-6: 0.61 pg/mL KC/GRO: 0.24 pg/mL IL-10: 0.95 pg/mL IL-12p70: 9.95 pg/mL TNF-α: 0.13 pg/mL
KIT#2: **Eotaxin, MIP-1beta, Eotaxin-3, TARC, IP-10, MIP-1alpha, IL-8, MCP-1, MDC, MCP-4**
Level of detection: Eotaxin: 3.26 pg/mL MIP-1β: 0.37 pg/mL Eotaxin-3: 1.77 pg/mL TARC: 0.22 pg/mL IP-10: 0.37 pg/mL MIP-1α: 3.02 pg/mL IL-8(HA): 95.6 pg/mL MCP-1: 0.09 pg/mL MDC: 1.22 pg/mL MCP-4: 1.69 pg/mL
KIT#3: **CRP, ICAM-1, SAA, VCAM-1**
Level of detection: SAA: 10.9 pg/mL CRP: 1.33 pg/mL VCAM-1: 6.00 pg/mL ICAM-1: 1.03 pg/mL
KIT#4: **TNFR1 and TNFR2**
TNF-R1: Intra-assay C.V.'s are 6.9%, 3.1%, and 4.2% at 61.01, 4426.3, and 3841.2 pg/mL respectively. TNF-R2: Intra-assay C.V.'s are 2.6%, 3.6%, and 3.4% at 126.6, 7158.6, and 6120.5 pg/mL respectively.

KIT#5: D-dimer
Level of detection: **110 - 2,000 ng/mL** The Immunochemical Core Laboratory at Mayo Clinic. The ICL is certified by both the College of American Pathologists (CAP# 1808201, AU ID#1183832) and the Department of Health and Human Services (CLIA ID# 24D0861265). Regulatory requirements include thorough test validation, documentation, standardized test procedures and review of quality control markers.

14.1.4 Analyses

Baseline chronic inflammatory mediator levels will be summarized and presented descriptively for all patients. The association between baseline chronic inflammatory mediator levels and the rate of adverse events and treatment modifications will be assessed graphically. Logistic regression models will also be utilized in an exploratory fashion to assess these associations. To examine the association between baseline chronic inflammatory mediator levels and the baseline geriatric assessment scores, we will use graphical means and Spearman's correlation coefficient. Exploratory linear regression models will also be utilized for this aim. The association between baseline chronic inflammatory mediator levels and the change in the geriatric assessment through time will be analyzed graphically and with exploratory repeated measures models.

14.2 Pharmacogenomics: (Alliance A171601-ST2): Genetic determinants of Palbociclib Efficacy and toxicity in the elderly

Alliance A171601-ST2 will evaluate genetic determinants of palbociclib efficacy and toxicity in elderly patients with estrogen receptor positive, HER2 negative metastatic breast cancer

14.2.1 Background

Multiple endocrine therapy options exist for treatment and prevention of breast cancer in post-menopausal women with estrogen receptor positive breast (HR positive) cancers.[98-100] Aromatase inhibitors (AI) such as letrozole, anastrozole and exemestane which function by inhibiting the aromatase enzyme (CYP19), have improved the recurrence rates of breast cancer after 5 years of tamoxifen treatment compared to placebo.[100] However, side effects notably musculoskeletal symptoms, from AI therapy have led to intolerance and subsequent discontinuation of treatment.[101-102] Data accumulated over the period now suggests that the benefits associated with prolonged endocrine therapy should be balanced with treatment tolerability and fracture risks[103]

Post-menopausal women with metastatic HR positive breast cancers are treated with fulvestrant which acts differently from the AIs by targeting the estrogen receptor. As an antagonist, fulvestrant binds to estrogen receptors competitively on tumors and other tissue targets, producing a nuclear complex that causes a dose-related down-regulation of estrogen receptors and inhibits tumor growth.[104] For advanced metastatic breast cancers exhibiting both HR-positive and human epidermal growth factor receptor 2 (HER2)-negative characteristics, improved progression free survival has been associated with treatment options that include an AI or fulvestrant together with a cyclin-dependent kinase (CDK) 4/6 inhibitor such as palbociclib.[105-107]

Palbociclib has been shown to specifically inhibit CDK 4/6 by blocking the progression of cells from G1 into S phase of the cell cycle and resulting in reduced cellular proliferation of ER-positive breast cancer cell lines [108,109]. Reports indicate that palbociclib enhances the

efficacy of cytostatic agents, such as endocrine therapy or HER2-targeted therapy, but decreases the efficacy of cytotoxic chemotherapy such as with carboplatin and doxorubicin [110-112]. Clinical trials have shown significant benefit in progression free survival for women with metastatic breast cancer on palbociclib with or without prior AI (letrozole) or fulvestrant treatment. The variation in median PFS among the patients have ranged from 10.2 months (95 % CI, 5.7–12.6) for the letrozole group to 20.2 months (95 % CI, 13.8–27.5) for the palbociclib-letrozole group suggesting that other factors associated with palbociclib could be contributing to the clinical outcomes.[105] Similar PFS trends were seen in the study of palbociclib with/without fulvestrant [106,107]. Turner et al.[106] reported a median PFS of 9.2 months (95 % CI, 7.5–not estimable) for palbociclib-fulvestrant group and 3.8 months (95 % CI, 3.5–5.5) for the placebo-fulvestrant group,[106,] while Cristofanilli et al[107]reported a median PFS of 9.5 months (95% CI, 9.2–11.0) in the palbociclib-fulvestrant group and 4.6 months (95% CI, 3.5–5.6) in the placebo-fulvestrant group.

All of these trials have shown variations in the clinical outcomes [105-107]. One factor that could in part explain some of these variations might be the role of inherited genetic variants whose proteins may be responsible for the biotransformation of the AIs, fulvestrant and palbociclib. Several reports on candidate genes and genome wide association studies (GWAS) have correlated single nucleotide polymorphisms (SNP) in the estrogen metabolism related pathway genes with response to endocrine therapy for breast cancer. [114-118] To date, there is no study that has looked at genetic variants associated with palbociclib biotransformation pathway genes with response to the treatment in metastatic breast cancer, let alone elucidate how these polymorphisms are associated with tolerability and response to palbociclib therapy in the elderly, specifically women aged 70 years and over. This proposal plans to elucidate the genetic determinants of palbociclib efficacy in post-menopausal women with metastatic HR positive, HER2 negative breast cancers undergoing treatment in the parent study.

Palbociclib metabolism, cell cycle proteins, genes and genetic variants: Palbociclib is primarily metabolized by CYP3A enzyme and undergoes sulfonation by SULT2A1 enzyme and undergoes acylation and glucuronidation as minor metabolic patheways.[109, 119-121]. Palbociclib is also a highly selective inhibitor of CDK4 and CDK6 kinases and in low nanomolar concentrations blocks retinoblastoma (Rb) gene protein product pRb.[108]

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that play a key role in regulating cell cycle progression by associating with cyclins. The cell cycle is a tightly regulated process of five distinct phases: G0 (quiescence) followed by G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-division) and M (cell division) with the G1 to S phase being the key checkpoint in protecting the cell from abnormal replication.[108] CDK4 and CDK6 interact with cyclin D1 early in this checkpoint phase resulting in the phosphorylation of pRb and allowing the release of transcription factor E2F which leads to transcription of other target genes to allow progression to the S phase.[108] CDK activity is thus tightly regulated at several levels by Cyclin D and retinoblastoma proteins and by CDK inhibitory proteins the INK4 family (p16, p15, p18, p19) and CIP/KIP family (p21, p27, p57).[122-124] Thus when the cell cycle regulatory mechanism is altered, uncontrolled cell proliferation occurs which is a distinctive feature of human cancers.[125]

Cell cycle genes, polymorphisms and cancer: Many of the genes encoding the cell cycle proteins are frequently mutated in human cancers and this leads to uncontrolled cell division and tumor growth as well.[126] For instance, in breast cancer, alterations in cell cycle regulators have been reported to include amplification of cyclin D1 gene (15-20% cancers) and overexpression of its protein product which has been associated with poor clinical outcomes, to indolent estrogen receptor positive phenotype and to tamoxifen resistance

cyclin D protein.[108, 127-132] Furthermore, studies have been reported that show that inhibiting CDK4 and CDK6 kinases induce G1 arrest in sensitive cell lines and primary bone marrow cells and prevent tumor growth in human myeloma xenografts.[133-137]

The genes encoding the proteins involved in the G1-S phase include *CCND1*[cyclin D1], *CCND2* [cyclin D2], *CCND3* [cyclin D3], *CCNE1* [cyclin E] (the cyclin family which regulate cyclin-dependent kinases); *CDK2* [p33], *CDK4*, and *CDK6* (cyclin-dependent kinases for the G_1/S transition); *CDKN1A* [p21, Cip1], *CDKN1B* [p27, Kip1] (CIP/KIP family cyclin-dependent kinase inhibitors); *CDKN2A* [p16], *CDKN2B* [p15], *CDKN2C* [p18], and *CDKN2D* [p19] (INK4 family cyclin-dependent kinase inhibitors) and *RB1* retinoblastoma gene. Studies relating to genetic polymorphisms in cell cycle genes and risk of some cancers including lung, bladder, prostate, breast, ovarian, endometrial, pancreas, and colorectal[138-145] have been published although none have taken into consideration the effects these inherited genetic variations may have on the efficacy of palbociclib which specifically inhibits the CDK4/6 check point.

In breast cancer studies, polymorphisms such as *CDKN1B* rs2066827 has been associated with shortened disease-free survival in patients with infiltrating metastasis-free breast cancer[146] while *CCND3* rs2479717 has been associated with an increased risk of death.[147] Other SNPs including *CCNE1* rs997669, *CDKN1A* rs3176336, *CDKN1B* rs34330, *CDKN2B* rs3218005 and *CDKN2A* rs3731239 have been associated with breast cancer as well.[148] *CCND1* rs9344 (*CCND1-02* A870G or *CCND1* G870A) the most studied SNP in *CCND1* and previously referred to as CCND1 rs603965 has been shown to be associated with breast cancer survival in Chinese subjects,[149] and has also been associated with breast cancer risk and poorer breast cancer specific survival in patients with metastatic breast cancer.[15-152] Polymorphisms in *CYP3A4*[153,154] and in *SULT2A1*[155,156] have also been associated with breast and other cancers.

These associations of the cell cycle gene SNPs with breast cancer may be influenced by palbociclib's action of inhibiting CDK4/6 in the G1-S transition point thereby modifying clinical response and toxicity outcomes. This study is ideal to elucidate the associations of cell cycle SNPs in the presence of palbociclib on breast cancer in the elderly. We note that polymorphisms in aromatase *CYP19A, CYP2A6* and estrogen receptor *ERS1* genes[157-160], the targets for AI inhibitors and fulvestrant respectively, have also been associated with breast cancer. Therefore SNPs in these 2 genes under the influence of their specific inhibitors combined with palbociclib in the treatment (choice of AI or fulvestrant made at the discretion of the treating investigator) will be studied for associations with clinical response and toxicity to palbociclib. Furthermore, the genetic variants in palbociclib related genes will be correlated with the primary objective of the study which includes tolerability (adverse events); and with the secondary objectives which include toxicity, response to treatment, and overall survival.

We hypothesize that inherited genetic polymorphisms in cell cycle pathway genes and in genes that metabolize palbociclib will correlate with clinical outcomes in elderly patients undergoing palbociclib treatment for estrogen receptor positive, HER2 negative metastatic breast cancer. We further hypothesize that genes in CYP19A1, CYP2A6 and ESR1 will also correlate will toxicity outcomes in this study.

We propose to achieve this hypothesis by genotyping patient DNA samples for SNPs in the cell cycle genes including **CCND1, CCND2, CCND3**, **CCNE1**, **CDK2**, **CDK4**, **CDK6**, **CDKN1A**, **CDKN1B**, **CDKN2A**, **CDKN2B, CDKN2C**, **CDKN2D**, ***CYP3A4, CYP19A1, CYP2A6, ESR1 RB1*** and ***SULT2A1*** and correlate these SNPs to efficacy and toxicity of palbociclib.

14.2.2 Objectives

- To explore whether inherited genetic single nucleotide polymorphisms (SNPs) in cell cycle pathway genes and in genes that metabolize palbociclib are associated with efficacy and toxicity in elderly patients undergoing endocrine plus palbociclib therapy for estrogen receptor positive, HER2 negative metastatic breast cancer.
- To explore whether SNPs in *CYP19A1, CYP2A6* and *ESR1* will also correlate with efficacy and toxicity in elderly patients undergoing endocrine plus palbociclib treatment for estrogen receptor positive, HER2 negative metastatic breast cancer.

14.2.3 Methods

Whole blood sample will be collected in 1 x10 mL EDTA vacutainer tube (purple top) from patients at start of study for germline DNA isolation. Blood samples will be sent to a central location at Mayo Clinic and DNA will be isolated in the Biospecimen Accessioning and Processing (BAP) laboratory(submission instructions are in Section 6.2)

SNP selection Genotype data from the National Center for Biotechnology Information (NCBI) dbSNP database will be used with programs in National Institute of environmental Health Sciences [redacted] Genome variation server [redacted] to derive tagged SNPs from the list of 18 genes namely **CCND1, CCND2, CCND3**, **CCNE1**, **CDK2**, **CDK4**, **CDK6**, **CDKN1A**, **CDKN1B**, **CDKN2A**, **CDKN2B, CDKN2C**, **CDKN2D**, ***CYP3A4, CYP19A1, CYP2A6, ESR1, RB1*** and ***SULT2A1***. SNPs with allele frequencies $\geq$ 30% and r2 $\geq$ 0.80 will be selected for genotyping. Since only 88 patients will be accrued for the study, this minor allele frequency (maf) cut off of 30% will ensure that we observe at least 10% of the patients with a SNP of interest. It is important to indicate here that the overall sample number of 88 is low, therefore any associations may serve as hypothesis generating for larger study numbers in the future. It is also important to note that there's ethnic variation in specific SNPs and their frequencies, therefore whenever the patient numbers are large enough to obtain meaningful information on diverse populations, genotype information from the database should reflect the patient population on the trial. The acquired tagSNPs (See Appendix VIII) will be genotyped in the Genotyping Core of the Mayo Clinic Medical Genome Facility (MGF) or in any Alliance associated genotyping core on either the Sequenom or the Illumina GoldenGate custom array. A partial list of tag SNPs to be genotyped is shown in the Table below:

Partial list of cell cycle pathway genes and SNPs to be genotyped

Gene	description	dbSNP rsid	Variant location/ function	Alleles		Global Minor allele frequency (MAF)
				Major	Minor	
CDK4	Cyclin dependent kinase 4	rs2069502	intron	C	T	0.3367
CDK6	Cyclin dependent kinase 4	rs2282978	intron	T	C	0.3141
CCND1	cyclin D1	rs9344	synonymous codon	G	A	0.413
CDKN1A	p21	rs3176336	intron	T	A	0.3678
CDKN1B	p27	rs34330	2KB upstream, 5UTR	C	T	0.3383
CDKN2A	p16	rs2811710	500B downstream, 3UTR	C	T	0.4708
CDKN2B	p15	rs3217992	3UTR, intron	C	T	0.3482
CDKN2D	p19	rs1465701	intron	C	T	0.4193

Genotyping

The Agena iPLEX (previously called sequenom) genotyping protocol involves PCR amplification of DNA using SNP specific primers, followed by a base extension reaction using the iPLEX Gold chemistry (Agena Biosciences, San Diego, CA). The protocol has been used for years and will briefly be described here. SNP-specific PCR and extension primers were designed and organized into pools with the Assay Design Suite (Agena). All primers were purchased from Integrated DNA Technologies (Coralville, IA). A QC run was performed with Coriell and CEPH controls, and results were tested for Mendelian inconsistencies. HotStar Taq Polymerase (Qiagen) was used for all PCRs. 15 ng of DNA was added to each 5-ul PCR reaction mixture in a 384-well microtiter plate. The PCR condition was 94°C for 15 min for hot start, followed by 45 cycles of denaturing at 94°C for 20 sec, annealing at 56°C for 30 sec, extension at 72°C for 1 min for 45 cycles, and final incubation at 72°C for 3 min. The PCR products were then treated with SAP (shrimp alkaline phosphatase, Agena) for 40 min at 37°C then ramped to 85°C for 5 min to remove excess dNTPs. The final base extension products were diluted in double distilled water and then treated with 6mg of SpectroCLEAN (Agena) resin per well to remove contaminating salts. 10-18 nl of treated extension product was spotted to the appropriate location on a 384-pad SpectroCHIP II (Agena) using a RS1000 Nanodispenser (Agena, San Diego, CA). A MassARRAY Analyzer Compact MALDI-TOF MS (Agena) was used for data acquisitions from the SpectroCHIP. All resultant genotyping calls were performed in real time by the MassARRAY Typer Analyzer v4.0.26.73 (Agena)

14.2.4 Analyses

SNP analysis: Results from genotyping will be sent to the bioinformatics/statisticians for analyses to correlate the SNPs with the primary objective of the study which is adverse events. The SNPs will also be correlated to the secondary objectives which include toxicity, response to treatment and overall survival.

14.2.5 Hypotheses

1. Patients with higher biomarker levels have an increased incidence of grade 3+ adverse events.
2. Patients with higher biomarker levels have higher rates of treatment modification during adjuvant therapy.
3. Patients with higher biomarker levels have poorer baseline performance status and higher rates of performance status decline during adjuvant therapy.

14.2.6 Statistical analyses

Treatment modification is defined as any dose reduction or omission during the course of the study. Biomarker levels will be compared to grade 3+ adverse event incidence (as measured by the CTCAE version 5.0), rate of treatment modification, baseline performance status and performance status throughout the course of the study descriptively and graphically. Any testing done will be done in an exploratory manner.

14.3 Pharmacokinetics: (Alliance A171601-PP1) Population Pharmacokinetics of Palbociclib

Alliance A171601- PP1 will evaluate if palbociclib exposure (AUC/C_{max}) is related to change from baseline in neutrophil numbers i.e. neutropenia.

14.3.1 Background and Hypotheses

Palbociclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). The FDA approved regimen is a 125 mg capsule of palbociclib taken orally once daily for 21 consecutive days followed by 7 days off treatment combined with letrozole 2.5 mg PO daily, on 28-day cycles.

Palbociclib is slowly absorbed with a Tmax of 6-12h following an oral 125 mg dose, with a mean C_{max} of 133 (+/-SD 18.6) ng/mL.. The terminal elimination half-life is mean 29 +/- 5 h, and steady state concentrations are usually reached in 8 days. The palbociclib is 85% bound to plasma proteins and its geometric mean apparent volume of distribution (Vz/F) was 2583 L with a coefficient of variation (CV) of 26%. The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.1 L/hr (29% CV). In 6 healthy male subjects given a single oral dose of ^{14}C- palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; feces (74.1% of dose) was the major route of excretion, with 17.5% of the dose recovered in urine. The majority of the material was excreted as metabolites.

Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of palbociclib exposure, which supports administration of palbociclib with food. Compared to palbociclib given under overnight fasted conditions, the population average area under the concentration-time curve from zero to infinity ($AUC_{(inf)}$) and C_{max} of palbociclib increased by 21% and 38%, respectively, when given with high-fat, high-calorie food (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), by 12% and 27%, respectively, when given with low-fat, low-calorie food (approximately 400 to 500 calories with 120, 250, and 28 to 35 calories from protein, carbohydrate, and fat, respectively), and by 13% and 24%, respectively, when moderate-fat, standard calorie food (approximately 500 to 700 calories with 75 to 105, 250 to 350 and 175 to 245 calories from protein, carbohydrate, and fat, respectively) was given 1 hour before and 2 hours after palbociclib dosing.

In vitro and in vivo studies indicate that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of ^{14}C palbociclib to humans, the primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma (23%). The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. Palbociclib was extensively metabolized with unchanged drug accounting for 2.3% and 6.9% of radioactivity in feces and urine, respectively. In feces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 26% of the administered dose. Data from a clinical trial in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were coadministered.

In vitro studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant SULT enzymes indicated that CYP3A and SULT2A1 are mainly involved in the

metabolism of palbociclib. In vivo, palbociclib exposure was increased by 1.9-fold when it was coadministered with itraconazole (strong CYP3A4 inhibitor), and co-administration of strong CYP3A4 inhibitors should be avoided. If co-administration with a strong CYP3A inhibitor cannot be avoided, the daily palbociclib dose should be reduced to 75 mg. In vivo, palbociclib exposure was decreased by 85% when it was coadministered with rifampin (strong CYP3A inducer), and co-administration of strong CYP3A inducers should be avoided. The effect of moderate CYP3A inducers on palbociclib exposure is not known, and co-administration of moderate CYP3A4 inducers should be avoided. Co-administration of palbociclib with multiple doses of rabeprazole (proton pump inhibitor) under fed conditions did not have a clinically significant effect on palbociclib exposure. In vitro, palbociclib caused time-dependent inhibition of CYP3A4. Palbociclib increased the midazolam (CYP3A substrate) AUC by 61% in healthy subjects, and therefore co-administration of sensitive CYP3A substrates with narrow therapeutic indices should be avoided.

Based on prior population pharmacokinetic analysis from male and female patients treated with palbociclib, neither gender, age nor body weight had a clinically important effect on palbociclib exposure. Furthermore, no dose reduction is needed in patients with mild or moderate renal impairment, or mild hepatic impairment. No clinically significant change in the QTc interval was detected when palbociclib was administered to steady state. Definitive conclusions regarding an exposure-response relationship for progression free survival (PFS) could not be made based on the limited data at a fixed dose of 125 mg from prior clinical studies. However, a greater reduction in absolute neutrophil count is suggested to be associated with increased palbociclib exposure. These exposure effect relationships for older patients (over 70 and over 75 years of age) have not been defined.

The primary hypothesis of this population-pharmacokinetic nested study is

(1) That palbociclib exposure (AUC/C_{max}) is related to change from baseline in neutrophil numbers i.e. neutropenia.

Secondary exploratory hypotheses are that palbociclib exposure is associated with (i) degree of thrombocytopenia in older patients (ii) progression free survival in older patients (iii) these relationships will be strengthened by consideration of known polymorphisms in palbociclib drug metabolizing enzymes (especially CYP3A and SULT-2A1) and drug transporters.

14.3.2 Objectives:

- To refine a population pharmacokinetic model (of Sun and Wang) using NONMEM for palbociclib taking account of relevant intrinsic and extrinsic factors.
- To determine the intrapatient and interpatient variability of palbociclib (AUC) in older breast cancer patients receiving palbociclib plus letrozole
- To explore the exposure (AUC/C_{max}) toxicity (neutropenia, thrombocytopenia) relationship for palbociclib when combined with letrozole in older breast cancer patients

14.3.3 Methods

For patients in the study who are receiving palbociclib plus letrozole or fulvestrant, venous blood samples for palbociclib concentrations will be obtained at baseline, and at the scheduled follow-up clinic visits on day 15 of cycle 1 and cycle 2, while still receiving study drug therapy. These samples will have the time of day they were obtained documented. At

these follow up visits a Patient Pharmacokinetic Questionnaire (see Appendix IX) will be filled in which will request information about the prior 48h dosing of palbociclib and the concomitant medications. This will detail the time of day the last two doses of study drug were taken, and relationship of when the doses were taken in relation to meals.

Palbociclib plasma concentrations will be measured using an LC-MS-MS assay validated in the Alliance Pharmacology/Pharmacokinetic core lab at the Univ. of Pittsburgh using a modification of the validated and published assay by Paul et al Biomed Chromatogr. 2018 Dec 13:e4469.

Pharmacokinetic population data modeling of the C_{min} (trough) drug concentrations will be performed using NONMEM to derive palbociclib specific AUCs and the intra and inter-patient variability (see below for details).

14.3.4 Statistical design:

The primary scientific hypothesis is that palbociclib exposure (AUC/C_{max}) is related to change from baseline in neutrophil numbers i.e. degree of neutropenia.

Population Pharmacokinetic Modeling: We will develop parametric population pharmacokinetics models for the exposure of palbociclib. To capture both between and within-subject variabilities in palbociclib exposures, a non-linear mixed effects model will be used. In particular, we will consider models of the form

$$yi\ [t]\ =\ \Psi\ [t, \theta, \eta i; D, x]\ +\ \varepsilon i\ [t]$$

where denotes yi [t] the observed plasma concentration at time t, t (t1,…, tk), obtained through sparse sampling as previously described, for the i-th individual and denotes the vector of population parameters of size p. The quantity D denotes the dose level and x is a vector of additional covariates. The random vectors i and = (i[t1],…, i[tk]) account for the between and within subject variabilities respectively. If possible, non-linearities with respect to time will be explored. The model will be fitted using first-order conditional maximum likelihood estimation in the NONMEM program (version 5)[161]. For this purpose it will be assumed that the random effects i…n are independent q-variate mean-zero normal random variables with common variance i where q is at most equal to p (the dimension of the population parameter vector θ). It is also assumed that the measurement errors 1,…,n are independent k-variate mean-zero normal vectors with common covariance matrix. Individual pharmacokinetic parameter estimates will be obtained from the estimated population PK model for palbociclib.

Covariate testing will be performed to identify sources of variability in exposure to palbociclib among individuals. Covariates that will be tested include: demographic characteristics, organ function markers, disease severity, genetic markers, and concomitant medications and time relationship to ingestion of the previous meal. All derived PK parameters will be summarized using standard numerical and graphical displays.

Pharmacometric Analyses:

Patients with pharmacokinetic, key toxicity and efficacy data will be included in the pharmacometric analyses. First a population pharmacokinetic approach will be employed to analyze the plasma concentration data for palbociclib. Relevant demographic and intrinsic /extrinsic factors will be explored for covariate relationship. Different empirical Bayesian PK parameters will be correlated initially with toxicity and later with efficacy endpoints such as the overall survival. Pharmacokinetic-biomarker relationships using key markers will also be conducted.

Population PK sampling schedule

Patients are scheduled to be reviewed in the clinic on Day 15 of cycle 1 and 2. Venous blood (5 ml) will be obtained at the time of these clinic visits and medical evaluations. Patients **MUST** be instructed **NOT** to take their palbociclib dose on the day of these visits before being seen and having this blood sample obtained. Blood will be collected into potassium EDTA (lavender top) tubes, and plasma separated by centrifugation at 1500 g for 10 minutes. Aliquots of plasma will then be placed in labelled polypropylene tubes (1 mL in each of two tubes) and stored at -70 to - 80 °C until shipped on dry ice to the Alliance Pharmacology/Pharmacokinetic core as indicated in Section 6.2.1.

15.0 General Regulatory Considerations and Credentialing

15.1 Geriatric Assessment Training

At each participating site, a research nurse or clinical research professional (CRP) (person who intends to administer the geriatric assessment) will receive training on administration of the geriatric assessment using the online video training module through the Alliance website, hyperlink below:

[redacted]

To login, select "Member Login" on the Alliance homepage and enter the CTEP-IAM account username and password. After logging in, the training module can be found under education and training > online training and under "For Site Staff." Once the training is complete, print a copy of the completion certificate to keep in the study records and submit it to CTSU according to Section 4.2.3. Training completed within the past two years is acceptable, as it is not study specific.

Any further questions or concerns regarding administering the geriatric assessment may be directed to the study chair.

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17.0 MODEL CONSENT FORM

Study Title for Study Participants:

Testing the effects of palbociclib and fulvestrant or letrozole for patients 70 years of age and older with metastatic breast cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Alliance A171601: A Phase II Trial Assessing the tolerability of Palbociclib in combination with letrozole or fulvestrant in patients aged 70 and older with estrogen receptor positive, HER-2 negative metastatic breast cancer

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What is the usual approach to my breast cancer?

We are asking you to take part in this study because you are 70 years old or over and have been recently diagnosed with estrogen receptor positive, HER2 negative metastatic breast cancer. Patients with this metastatic breast cancer are usually treated with a drug called palbociclib along with a hormonal agent, either fulvestrant or letrozole, as determined by your doctor. Palbociclib and letrozole are given by mouth and fulvestrant is an injection. This study follows the usual Food and Drug Administration (FDA) approved treatment, but we are conducting this study because we don't know if older patients have more side effects than younger patients.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above without being in a study.
- You may choose to take part in a different study, if one is available.
- You may choose not to be treated for cancer and may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to find out the side effects that the standard, FDA-approved combination treatment of letrozole or fulvestrant and palbociclib has on patients 70 years old and over. Palbociclib given along with letrozole or fulvestrant instead of letrozole or fulvestrant

alone seems to prevent the cancer from getting worse. However, few patients aged 75 and older participated in previous studies. There will be about 88 people taking part in this study.

What are the study groups?

In this study, all study participants will get the same treatment. You will take one capsule of palbociclib once a day with food for 21 days. You will not take palbociclib for the next 7 days. This 28 day period is called a cycle. You should try to take the palbociclib capsules at about the same time each day. You should not have grapefruit or grapefruit juice while on this study. You should also check with your doctor or pharmacist before using any new medicines, including over-the-counter drugs because of possible drug interactions.

During this period, you will also be given either letrozole or fulvestrant based on what your doctor decides. If your doctor prescribes letrozole, you will take one pill daily for 28 days. If your doctor prescribes fulvestrant you will receive injections on the first day and fifteenth day of the first cycle and then on the first day of every cycle after that. You will continue on this treatment plan until your cancer progresses or if you have side effects that may prevent you from continuing to take the treatment.

Each cycle is 28 days (4 weeks)

Palbociclib plus Letrozole

	Week 1	Week 2	Week 3	Week 4	Week 5+
Palbociclib	1 capsule every day	1 capsule every day	1 capsule everyday	No capsule	1 capsule every day for 21 days, then 7 days no capsules
Letrozole	1 pill every day	1 pill every day	1 pill every day	1 pill every day	1 pill every day for 28 days

If you forget to take a capsule of palbociclib or letrozole, do not make up the missed dose. Skip that dose and take the drug on the next day.

Or

Palbociclib plus Fulvestrant

	Week 1	Week 2	Week 3	Week 4	Weeks 5+
Palbociclib	1 capsule every day	1 capsule every day	1 capsule everyday	No capsule	1 capsule every day for 21 days, then 7 days no capsules
Fulvestrant	Injection on Day 1	No injection	Injection on Day 15	No injection	Injection on Day 1 of every 28-day cycle

If you forget to take a capsule of palbociclib, do not make up the missed dose. Skip that dose and take the capsule on the next day.

How long will I be in this study?

You will receive the study treatment for as long as you do not have severe side effects and your cancer does not get worse. If you develop severe side effects or your cancer gets worse, your doctor may decide to remove you from the study treatment. After you stop the study treatment, your doctor will continue to follow your progress every year for up to five years.

What extra tests, and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra questionnaires that you will need to complete if you take part in this study.

You will be asked to complete four questionnaires and perform some tasks as part of this study. The questionnaires will be used in this study in order to find out more about how you feel during cancer treatment and what the effect of the treatment may be.

The questionnaires will be completed at the following time points:

Geriatric Assessment: You will be asked to complete the geriatric assessment before you begin treatment, prior to cycle 4, and at the end of your treatment period. It will take about 30 minutes to complete. The geriatric assessment involves a questionnaire, an interview and a task. Some questions will be asked by a member of the health care team. You will complete other questions on your own. If you have difficulty completing any of the questions or tasks, a member of the team will help you. You may skip any questions you do not wish to answer. The walking task involves minimal risk. It will involve you getting up from a chair, walking 10 feet, and returning to the chair. Possible risks include feeling tired, dizziness, increased heart rate, and falling. To minimize this risk you will be closely monitored by a member of the health care team during this task. If you are uncomfortable with walking, you may skip this task.

You will be asked to complete three other questionnaires, two of which will be required at the beginning of every cycle for the first 6 cycles of treatment, and at the end of your treatment period. These questionnaires will involve questions about the side effects you are experiencing from your treatment and about your general quality of life. They will take about fifteen to twenty minutes to complete. The other questionnaire will only need to be completed at the end of your treatment. It will ask questions regarding how the study helped you. It will take about five minutes to complete.

Pill Diary
You will also be completing a pill diary every day, for the first three cycles. You will be asked to bring the completed pill diary at the end of every cycle, to make sure you are taking the correct dose and not more than the standard dose.

You will receive routine scans every 12 weeks to see if your cancer is getting worse or better, as part of your cancer care. Your doctor will send copies of these scans to the Alliance, so that researchers can evaluate whether the treatment you are receiving may cause loss of muscle tissue.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may be serious and may even result in death.

You can ask the study doctor questions about side effects at any time. Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different, so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. Keep in mind that there might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of Palbociclib, Letrozole and Fulvestrant:

Possible Side Effects for Palbociclib (PD-0332991)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Palbociclib (PD-0332991), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Nausea • Tiredness • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Palbociclib (PD-0332991), from 4 to 20 may have:
• Blurred vision, watering eyes • Dry eye, skin • Constipation, diarrhea, vomiting • Sores in the mouth which may cause difficulty swallowing • Fever • Bruising, bleeding • Loss of appetite • Changes in taste • Headache • Nose bleed • Hair loss, rash

RARE, AND SERIOUS In 100 people receiving Palbociclib (PD-0332991), 3 or fewer may have:
• Damage to the lungs which may cause shortness of breath

Possible Side Effects of Fulvestrant

COMMON, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, more than 20 and up to 100 may have:
• Pain • Tiredness • Increased sweating • Hot flashes, flushing • Swelling and redness at the site of the medication injection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, from 4 to 20 may have:
• Constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn • Swelling of the body • Loss of bone tissue, broken bone, or decreased height • Dizziness, headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, from 4 to 20 may have:
• Difficulty sleeping • Fluid around lungs • Swelling of the liver which may cause belly pain • Worry, depression, mood swings • Hair thinning • Cough

RARE, AND SERIOUS In 100 people receiving Fulvestrant, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Liver damage which may cause yellow eyes and skin • Vaginal bleeding • Blood clot which may cause swelling, pain, shortness of breath • Heart attack or heart failure which may result in chest pain, shortness of breath, swelling of ankles, and tiredness • Stroke which may cause weakness, paralysis

Possible Side Effects of Letrozole

COMMON, SOME MAY BE SERIOUS In 100 people receiving Letrozole, more than 20 and up to 100 may have:
• Pain • Tiredness • Increased sweating • Hot flashes, flushing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Letrozole, from 4 to 20 may have:
• Constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn • Swelling of the body • Loss of bone tissue, broken bone, or decreased height • Dizziness, headache • Difficulty sleeping • Fluid around lungs • Swelling of the liver which may cause belly pain • Worry, depression, mood swings • Hair thinning

RARE, AND SERIOUS In 100 people receiving Letrozole, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Liver damage which may cause yellow eyes and skin • Vaginal bleeding • Blood clot which may cause swelling, pain, shortness of breath • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Stroke which may cause weakness, paralysis

Risks from questionnaires
You may become tired from the amount of time needed to fill out the questionnaires and do the other evaluations. The questionnaire will focus on life issues that could cause you to become emotionally upset. If you become distressed a member of the study team will talk with you. If needed, you can be referred to your doctor to determine how best to handle your concerns.

Risks from walking task
As part of the geriatric assessment, you will be asked to complete a walking task. You may feel tired, dizzy, have an increased heart rate or fall during the walking task. To minimize this risk, you will be closely monitored by a member of the health care team during this task. If you are uncomfortable with walking, you may skip this task.

What possible benefits can I expect from taking part in this study?
This study may or may not help you. However, this study may help us understand how this study drug works in older adults, and may help researchers learn things that may help other older people in the future.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In turn, the study doctor may remove you from the study, if:
- Your health changes and the study is no longer in your best interest
- New information becomes available
- You do not follow the study rules
- The study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number).*

What are the costs of taking part in this study?

Your Potential Costs:

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You and/or your health plan/insurance company will be responsible for:

- Palbociclib, letrozole or fulvestrant and all premedications, fluids and procedures.
- Exams, tests, and procedures that may be needed to manage side effects and to monitor your safety.

Costs Paid by the Study

Exams, tests, and procedures done for research purposes only will not be billed to you or your insurance plan. These include blood collections for the optional studies and submission of images to the Alliance for evaluating whether the treatment you are receiving may cause loss of muscle tissue.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you have legal rights to receive payment for this injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case.

However, your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information and information about your specimen from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the database may also be shared with these organizations. They are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance for Clinical Trials in Oncology
- The NCI Central IRB is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. Once the study is over, the site may include a summary of the results. This summary will not include any information that can identify you.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Additional Studies Section:
This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

Neither you nor your insurance will be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the optional studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for laboratory studies and biobanking for possible future studies

Researchers are trying to learn more about cancer and other health problems using samples from people's tissue, blood, urine, or other fluids. By conducting research on these samples, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about how genes affect health and disease and how people respond to treatment. Genes carry information about features that are found in you and your family, from the color of your eyes to health conditions for which you may be at risk. Research that studies your genes is known as genomics or genetics.

If you choose to take part in these optional studies, the study doctor for the main study would like to collect blood for research on why patients have different side effects from the treatment.

In addition, the researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The additional research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the Alliance and supported by the National Cancer Institute.

What is involved?

If you agree to take part, here is what will happen next:

1) About 6 teaspoons of blood will be collected from a vein in your arm. Four teaspoons of blood will be drawn before you begin treatment, and two teaspoons will be drawn after you have taken three cycles of treatment.
2) In addition, one teaspoon of blood will be collected before you start study treatment, at your cycle 1 day 1 and day 15 clinic visits, and cycle 2 day 15 clinic visit, for research on how the study drug changes in your body over time and if that can change your side effects. You will also complete a form at these visits when blood is collected for this research. It will take less than five minutes to complete this form. For this study, your blood will be sent to researchers at the University of Pittsburgh Cancer Center with your initials and collection date and time on it.
3) Your baseline blood sample and some related health information will be sent to a researcher for use in the study described above. Remaining baseline blood samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
4) Only qualified researchers can receive samples from the biobank. There will be scientific and ethics reviews to ensure that the research is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
5) Neither you nor your study doctor will be notified when research will be conducted. You will not receive reports or other information about any research that is done using your samples.
6) Some of your genetic and health information may be placed in central databases that will be available to qualified researchers. Information that could directly identify you will not be included.

What are the possible risks?

1) The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
2) Even without your name or other identifiers, your genetic information is unique to you. There is a risk that someone outside of the research could get access to your personal information in your medical records or trace information in a database back to you. The researchers believe the chance that someone could re-identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent by the biobank to the qualified researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Your blood sample collected for one of the additional studies will be sent to researchers at the University of Pittsburgh Cancer Center with your initials and collection date and time on it.
4) Researchers to whom the Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
5) Information that identifies you will not be given to anyone, unless required by law.
6) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the biobank will no longer be used and related health information will no longer be collected. This will not apply to those samples or related information that have already been given to or used by qualified researchers.

What if I have questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

Samples for the laboratory studies:

1. I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory studies described above.

   YES NO

Samples for future research studies:

2. My samples and related information may be kept in a biobank for use in future health research.

   YES NO

3. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the main study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX I: PATIENT INFORMATION SHEETS

Patient Completed Booklet A: Cycle 1 and 4, Day 1

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on Day 1 of Cycle 1 and 4 of your study treatment. It contains the following questionnaires:

    - Geriatric Assessment
    - EQ-5D 3L
    - PRO-CTCAE questionnaire Day 1
    - Geriatric Assessment: Healthcare Professional Questionnaire
        -**Note: This form is to be completed by the healthcare professional, not the patient.**

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet B: Cycles 1 and 2, Day 15

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on Day 15 of Cycles 1 and 2 of your study treatment. It contains the following questionnaires:

    - PRO-CTCAE questionnaire Day 15

2. Directions on how to complete each set of questions are written on the top of each set.

3. It is very important that you return the booklets to us, whether you finish the study or not.

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet C: Cycle 2, Day 1, and Cycles 3, 5, and 6

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on Day 1 of Cycle 2, and Cycles 3, 5, and 6 of your study treatment. It contains the following questionnaires:
    - EQ-5D 3L
    - PRO-CTCAE questionnaire Day 1
2. Directions on how to complete each set of questions are written on the top of each set.
3. It is very important that you return the booklets to us, whether you finish the study or not.
4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.
5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Booklet D: END OF TREATMENT

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed at the end of your treatment. It contains the following questionnaires:
    - Geriatric Assessment
    - PRO-CTCAE questionnaire
    - EQ-5D 3L
    - Was it Worth It Questionnaire
    - Geriatric Assessment: Healthcare Professional Questionnaire
        -Note: This form is to be completed by the healthcare professional, not the patient.
2. Directions on how to complete each set of questions are written on the top of each set.
3. It is very important that you return the booklets to us, whether you finish the study or not.
4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.
5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

APPENDIX II: GERIATRIC ASSESSMENT

GERIATRIC ASSESSMENT SURVEY

To be completed by Physician, Nurse, or CRA:
Responsible person name (*Physician, Nurse, or CRA*) _____

Assessment Period (as applicable to this study) ☐ Pre-treatment ☐☐ Cycle # ☐ End of Treatment

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PATIENT QUESTIONNAIRE

Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

☐ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) ☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? *(Mark one with an X.)*

□ 8th grade or less
□ 9-11th grade
□ High school graduate/GED
□ Associate degree/some college
□ Vocational/ technical school
□ Bachelor's degree
□ Advanced degree
□ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*

☐ Married
☐ Domestic partnership
☐ Widowed
☐ Divorced
☐ Separated
☐ Never married
☐ I prefer not to answer

3. With whom do you live? *(Mark all that apply with an X.)*

☐ Spouse / partner
☐ Girlfriend / boyfriend
☐ Children aged 18 years or younger
☐ Children aged 19 years or older
☐ Parent(s)/parent(s)-in-law
☐ Live alone
☐ Others, specify: _____
☐ Other relative, specify: _____

4. What is your current employment status? *(Mark one with an X.)*

☐ Employed 32 hours or more per week
☐ Unemployed
☐ Employed less than 32 hours per week
☐ Retired
☐ Homemaker
☐ Full-time student
☐ Disabled
☐ Part-time student
☐ On medical leave
☐ Other, specify: _____

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone…
   - ☐ without help, including looking up and dialing;
   - ☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
   - ☐ are you completely unable to use the telephone?

2. Can you get to places out of walking distance…
   - ☐ without help (can travel alone on busses, taxis, or drive your own car);
   - ☐ with some help (need someone to help you or go with you when traveling); or
   - ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   - ☐ without help (taking care of all shopping needs yourself, assuming you have transportation);
   - ☐ with some help (need someone to go with you on all shopping trips); or
   - ☐ are you completely unable to do any shopping?

4. Can you prepare your own meals…
   - ☐ without help (plan and cook full meals yourself);
   - ☐ with some help (can prepare some things but unable to cook full meals yourself); or
   - ☐ are you completely unable to prepare any meals?

5. Can you do your housework…
   - ☐ without help (can clean floors, etc);
   - ☐ with some help (can do light housework but need help with heavy work); or
   - ☐ are you completely unable to do any housework?

6. Can you take your own medicines…
   - ☐ without help (in the right doses at the right time);
   - ☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - ☐ are you completely unable to take your medicines?

7. Can you handle your own money…
   - ☐ without help (write checks, pay bills, etc.);
   - ☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   - ☐ are you completely unable to handle money?

* OARS IADL[33]

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? (***Mark an X in the box on each line that best reflects your situation.***)

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities such as: running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities such as: moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

* MOS, Physical Functioning Scale[34]

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

☐ Normal, no complaints, no symptoms of disease

☐ Able to carry on normal activity, minor symptoms of disease

☐ Normal activity with effort, some symptoms of disease

☐ Care for self, unable to carry on normal activity or do active work

☐ Require occasional assistance but able to care for most of personal needs

☐ Require considerable assistance for personal care

☐ Disabled, require special care and assistance

☐ Severely disabled, require continuous nursing care

* Patient KPS[35]

E. FALLS

How many times have you fallen in the last 6 months? ☐☐☐

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at all, Somewhat or A Great Deal?** *(Mark an X in the box that best reflects your answer.)*

				If you have this illness: How much does it interfere with your activities?		
Illness	**No**	**Yes**		**Not at all**	**A little**	**A great deal**
a. Other cancers or leukemia	☐	☐	→	☐	☐	☐
b. Arthritis or rheumatism	☐	☐	→	☐	☐	☐

Illness	No	If you have this illness: How much does it interfere with your activities? Yes		Not at all	A little	A great deal
c. Glaucoma	☐	☐	→	☐	☐	☐
d. Emphysema or chronic bronchitis	☐	☐	→	☐	☐	☐
e. High blood pressure	☐	☐	→	☐	☐	☐
f. Heart disease	☐	☐	→	☐	☐	☐
g. Circulation trouble in arms or legs	☐	☐	→	☐	☐	☐
h. Diabetes	☐	☐	→	☐	☐	☐
i. Stomach or intestinal disorders	☐	☐	→	☐	☐	☐
j. Osteoporosis	☐	☐	→	☐	☐	☐
k. Liver disease	☐	☐	→	☐	☐	☐
l. Kidney disease	☐	☐	→	☐	☐	☐
m. Stroke	☐	☐	→	☐	☐	☐
n. Depression	☐	☐	→	☐	☐	☐

* OARS IADL[33]

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*

☐ Excellent

☐ Good

☐ Fair

☐ Poor

☐ Totally blind

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*

☐ Excellent

☐ Good

☐ Fair

☐ Poor

☐ Totally deaf

4. Do you have any other physical problems or illnesses (other than listed in questions 1-4) at the present time that seriously affect your health?

☐ No

☐ Yes, specify: ____

If yes, how much does this interfere with your activities? *(Mark one with an X.)*

☐ Not at all ☐ Somewhat ☐ A great deal

* OARS IADL[33]

G. NUTRITIONAL STATUS

1. Have you lost weight involuntarily over the past 6 months?

☐ No

☐ Yes

If yes, how much?

☐☐☐ pounds

2. What is your weight now?

☐☐☐ pounds

3. What was your weight 6 months ago?

☐☐☐ pounds

H. HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

How much of the time during the past month:	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
1. has your daily life been full of things that were interesting to you?	☐	☐	☐	☐	☐	☐
2. did you feel depressed?	☐	☐	☐	☐	☐	☐
3. have you felt loved and wanted?	☐	☐	☐	☐	☐	☐
4. have you been a very nervous person?	☐	☐	☐	☐	☐	☐
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	☐	☐	☐	☐	☐	☐
6. have you felt tense or high-strung?	☐	☐	☐	☐	☐	☐
7. have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
8. have you felt emotionally stable?	☐	☐	☐	☐	☐	☐
9. have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐

12. have you felt cheerful, light-hearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. were you a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐
16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

* MHI-17[34] - Stewart, A.L. and Ware, J.E., 1992

I. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? *(Mark one with an X.)*

   ☐ All of the time
   ☐ Most of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*

   ☐ Much less socially active than before
   ☐ Somewhat less socially active than before
   ☐ About as socially active as before
   ☐ Somewhat more socially active as before
   ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? *(Mark one with an X.)*

   ☐ Much more limited than others
   ☐ Somewhat more limited than others
   ☐ About the same as others
   ☐ Somewhat less limited than others
   ☐ Much less limited than others

* MOS, Social Activities[34]

J. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1. Someone to help you if you were confined to bed.	☐	☐	☐	☐	☐
2. Someone you can count on to listen to you when you need to talk.	☐	☐	☐	☐	☐
3. Someone to give you good advice about a crisis.	☐	☐	☐	☐	☐
4. Someone to take you to the doctor if needed.	☐	☐	☐	☐	☐
5. Someone to give you information to help you understand a situation.	☐	☐	☐	☐	☐
6. Someone to confide in or talk to about yourself or your problem.	☐	☐	☐	☐	☐
7. Someone to prepare your meals if you were unable to do it yourself.	☐	☐	☐	☐	☐
8. Someone whose advice you really want.	☐	☐	☐	☐	☐
9. Someone to help you with daily chores if you were sick.	☐	☐	☐	☐	☐
10. Someone to share your most private worries and fears with.	☐	☐	☐	☐	☐
11. Someone to turn to for suggestions about how to deal with a personal problem.	☐	☐	☐	☐	☐
12. Someone who understands your problems.	☐	☐	☐	☐	☐

* MOS Social Support Survey [36]

K. SPIRITUALITY/RELIGION*

Directions: Please answer the following questions about your religious beliefs and/or involvement. (Please mark an "X" in the box on each line that best reflects your situation.)

1. How often do you attend church, synagogue, or other religious meetings? *(Mark one with an X.)*

☐ More than once per week
☐ Once a week
☐ A few times a month
☐ A few times a year
☐ Once a year or less
☐ Never

2. How often do you spend time in private religious activities, such as prayer, meditation, or Bible study? *(Mark one with an X.)*

☐ More than once a day
☐ Daily
☐ Two or more times per week
☐ Once a week
☐ A few times a month
☐ Rarely or never

The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.

3. In my life, I experience the presence of the Divine (i.e., God). *(Mark one with an X.)*

☐ Definitely true of me
☐ Tends to be true
☐ Unsure
☐ Tends *not* to be true
☐ Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life. *(Mark one with an X.)*

☐ Definitely true of me
☐ Tends to be true
☐ Unsure
☐ Tends *not* to be true
☐ Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*

☐ Definitely true of me
☐ Tends to be true
☐ Unsure
☐ Tends *not* to be true
☐ Definitely *not* true

*DUREL: Duke University ReligionIndex[37] – Koenig et al., 1997

L. YOUR FEELINGS*

1. Do you often feel sad or depressed? *(Mark one with an X.)*

☐ No ☐ Yes

2. How would you describe your level of anxiety, on average? Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

0	1	2	3	4	5	6	7	8	9	10
No anxiety										Anxiety as bad as It can be

*Mahoney et al., 1994; LASA[38]

M. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand? ☐ No ☐ Yes
If Yes, which questions were they?

2. Was the time it took to answer all the questions too long, just right or too short?

☐ Too short → How long would you have liked the questionnaire to be? ☐☐ minutes

☐ Just right

☐ Too long → How long would you have liked the questionnaire to be? ☐☐ minutes

Which items would you remove?

3. Did you find any of the questions upsetting? ☐ No ☐ Yes

If Yes, which questions were they?

Could you tell me why they were upsetting?

4. Do you think the questionnaire left out any questions that were important to ask?

Thank you for your participation.

Geriatric Assessment: Healthcare Professional Questionnaire

To be completed by Physician, Nurse, or CRA

I. This form completed by: ***(Mark all that apply with an X.)*** Assessment Period (as applicable to this study)

☐ Physician ☐ Nurse ☐ CRA ☐ Pre-treatment ☐☐ Cycle # ☐ End of Treatment

☐ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) ☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

II. FUNCTIONAL STATUS

A. KPS (Healthcare professional rated*)
Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. *(Scale is listed below.)*

☐☐☐ %

%	CRITERIA
100	Normal: no complaints; no evidence of disease.
90	Able to carry on normal activity; only minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

* Physician KPS[39]

B. Timed "Up and Go"*

INSTRUCTIONS: The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go" ☐☐.☐ seconds

* Timed "Up and Go"[40]

III. COGNITION ***This section is only completed Pretreatment and at the end of treatment***

6-ITEM ORIENTATION-MEMORY-CONCENTRATION TEST**					
	Patient's Response	**Maximum errors**	**Score**	**Weight**	**Final score**
1. What <u>year</u> is it now? [without looking at a calendar]	☐☐☐☐	1	☐☐ x	4 =	☐☐
2. What <u>month</u> is it now? [without looking at a calendar]	☐☐	1	☐☐ x	3 =	☐☐
Memory Phrase: Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'					
3. About what <u>time</u> is it? [within 1 hour – without looking at your watch]	☐☐:☐☐	1	☐☐ x	3 =	☐☐
4. <u>Count</u> backwards 20 to 1.		2	☐☐ x	2 =	☐☐
5. Say the months in reverse order.		2	☐☐ x	2 =	☐☐
6. Repeat the Memory Phrase.		5	☐☐ x	2 =	☐☐
				TOTAL SCORE:	☐☐

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.

** OMC – Katzman, R., et al., 1983; Kawas, C., et al., 1995

IV. SCORING ***This section is only applicable if OMC-Test is completed Pretreatment and Post treatment***

Did the patient score ≥11 on the 6-Item Orientation-Memory-Concentration Test?

☐ No

☐ Yes (**If yes, notify the patient's treating physician.)**

This question is only applicable to question #1 in "Section K. Your Feelings" from the Patient Questionnaire.

1. How did the patient answer the question "Do you often feel sad or depressed?" in the Patient Questionnaire *(Section K)*?

   ☐ No

   ☐ Yes **(If yes, notify the patient's treating physician.)**

V. NUTRITION

What is the patient's height? (*from patient's chart*) ☐☐☐ cm

What is the patient's current weight? (*from patient's chart*) ☐☐☐ kg

What was the patient's weight approximately 6 months ago? *(from patient's chart or patients self report)* ☐☐☐ kg

Calculated Body Mass Index: ☐☐.☐

Percent Unintentional Weight Loss: ☐☐.☐%

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

A. Were any of the questionnaires in the "Geriatric Assessment – Healthcare Professional Questionnaire" difficult for you to administer?

☐Yes ☐No

If no, please proceed to the next question.

If yes, please indicate which questionnaire was difficult to administer? *(Mark all that apply with an X.)*

- ☐ KPS Healthcare Professional Rated (page 1)
- ☐ Timed Up and Go (page 2)
- ☐ 6-Item Orientation-Memory-Concentration Test (page 2)
- ☐ Other: Please specify _____

B. Were any of the questionnaires in the "Geriatric Assessment – Patient Questionnaire" difficult for the patient to complete?

☐Yes ☐No

B. If no, please proceed to the next question. If yes, please indicate which questionnaire(s) was difficult for the patient to complete? *(Mark all that apply with an X.)*

- ☐ Background Information (page 1)
- ☐ Daily Activities (page 2-3)
- ☐ Physical Activities (page 3)
- ☐ Current Health Rating (page 4)
- ☐ Falls (page 4)
- ☐ Your Health (page 4-5)
- ☐ Nutritional Status (page 7-8)
- ☐ Health Questionnaire (page 9)
- ☐ Social Activities (page 10)
- ☐ Social Support (page 11)
- ☐ Spirituality or religion (page 12)
- ☐ Your Feelings (page 13)

C. Was the patient able to complete "Geriatric Assessment – Patient Questionnaire" on his/her own?

☐Yes ☐No

If no, why? *(Mark all that apply with an X.)*

- ☐ Not literate (does not read or write)
- ☐ Visual problem
- ☐ Fatigue

☐ Questions too difficult (above the patient's reading ability)

☐ Other: specify_____

D. Length of time to complete both the Patient and Healthcare Professional Questionnaires

Length of time to complete healthcare professional questionnaire ☐☐☐ minutes

Length of time to complete patient questionnaire ☐☐☐ minutes

Total length of time to complete both questionnaires ☐☐☐ minutes

Completed by: _____ Date form completed: ☐☐ / ☐☐ / ☐☐☐☐

(Last name, First name) *M M D D Y Y Y Y*

APPENDIX III : WAS IT WORTH IT QUESTIONNAIRE

To be completed by Physician, Nurse, or CRA:

Patient Name: _____ Date: _____

Patient Number: _____

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

1. Was it worthwhile for you to participate in this research study? Y N U

2. If you had to do it over, would you participate in this research study again? Y N U

3. Would you recommend participating in this research study to others? Y N U

4. Overall, did your quality of life change by participating in this research study? *(circle one response)*

It improved It stayed the same It got worse

5. Overall how was your experience participating in this research study? *(circle one response)*

Better than I expected The same as I expected Worse than I expected

6. If there was one thing that could have been done to improve your experience in this research study, what would it be?

---

7. Would you like to talk to someone about your concerns? Yes No

(circle one response)

APPENDIX IV: OVERALL TREATMENT UTILITY

OTU is a novel clinical outcome measure incorporating objective and subjective measures of anticancer efficacy, tolerability, and acceptability, assessed at the end of treatment and condensed into a simple 3 point score.

OTU may be regarded as asking the clinician: "With the benefit of hindsight, are you glad you gave this treatment?" and asking the patient: "With the benefit of hindsight, are you glad you received it?". OTU is scored as good, intermediate or poor, corresponding to "yes", "uncertain" or "no" replies to these questions.

To score the OTU, the patient is assessed at the end of treatment, using the following criteria:

1) **Clinical benefit?** Categorized as:

    a. Both radiologically progression- free (RECIST response or stable disease) and no clinical deterioration as assessed by treating consultant

    b. Either radiologically progression- free (RECIST progressive disease) or clinical deterioration as assessed by treating consultant

2) **Tolerable and acceptable?** Categorized as:

    a. All of the following:

        - No SAE or SUSAR attributed to treatment
        - No episodes of grade ≥3 non-hematological toxicity
        - Patient response to "Which one of the following phrases best describes you at this time?" in section D of the Geriatric Assessment at the end of treatment is not "Require considerable assistance for personal care", "Disabled, require special care and assistance" or "Severely disabled, require continuous nursing care."
        - Patient response to "Was it worthwhile for you to undergo this cancer treatment?" from the Was It Worth It questionnaire is "Y"

    b. Any of the following:

        - An SAE or SUSAR (suspected unexpected serious adverse reaction) attributed to treatment
        - An episode of grade ≥3 non-hematological toxicity
        - Patient response to "Which one of the following phrases best describes you at this time?" in section D of the Geriatric Assessment at the end of treatment is "Require considerable assistance for personal care", "Disabled, require special care and assistance" or "Severely disabled, require continuous nursing care."

- Patient response to "Was it worthwhile for you to undergo this cancer treatment?" from the Was It Worth It questionnaire is not "Y"

Scoring:

Good OTU: Patient is alive and scores 1a/2a

Intermediate OTU: Patient is alive and scores 1a/2b or 1b/2a

Poor OTU: Patient is alive and scores 1b/2b, or patient is dead

APPENDIX V: EQ-5D-3L HEALTH QUESTIONNAIRE

EQ-5D-3L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑

I have moderate problems walking ❑

I am confined to bed ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

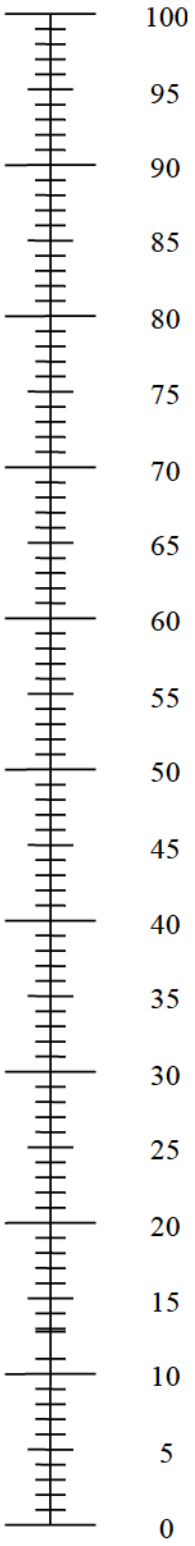
ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.



YOUR HEALTH TODAY = ☐

APPENDIX VI: PRO-CTCAE * -NCI-PRO-CTCAE TM ITEMS

Item Library version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days.

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

5.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

9.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly

10.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

11.	In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

12.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

16.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

17.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

18.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

19.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

20.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

21.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

22.	In the last 7 days, what was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST?						
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not sexually active	○ Prefer not to answer

23.	In the last 7 days, how OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

24.	In the last 7 days, how OFTEN did you have HOT FLASHES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HOT FLASHES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

APPENDIX VII: PATIENT MEDICATION DIARY - PALBOCICLIB

Today's date _____

Patient Name_____(initials acceptable) **Patient Study ID** _____

	INSTRUCTIONS TO THE PATIENT: 1. Complete this form while you take palbociclib and if you are taking letrozole. This form is a 28 day diary. You don't need to complete the letrozole column if you are not taking it. You may need to complete more than one form between clinic visits. 2. You will take your dose of palbociclib daily for 21 days. You will also take your dose of letrozole daily for 28 days. 3. Palbociclib interacts with other medications. Do not start any new prescription or over the counter medications without discussing with your doctor or pharmacist. 4 Take the palbociclib capsule with food at about the same time every day. Letrozole can be taken once daily without regard to food. 5. Record the date, and when you took the capsule and pill. Record doses as soon as you take them; do not batch entries together at a later time. 6. If you vomit or miss a dose, do not make up that dose; resume dosing with the next scheduled dose at the usual time. 7. Swallow capsule whole, do not crush or chew. It should be taken in combination with endocrine therapy (if taking Letrozole). The combination that you are being treated with may be palbociclib along with letrozole pill or fulvestrant injection. Do not take grapefruit or grapefruit juice when you are taking this drug. 8. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: 10:30 am SB 9:30 am 9. If you don't take your palbociclib dose for any reason, contact your physician. 10. Please return this form to your physician at your next appointment. You may need to return more than one form per clinic visit.

Day	Date	Time of daily dose- Palbociclib(21 days)	Time of daily dose- Letrozole(28 days)	If you missed a dose, Reason for not taking the capsule	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22		**No capsule**			
23		**No capsule**			
24		**No capsule**			
25		**No capsule**			
26		**No capsule**			
27		**No capsule**			
28		**No capsule**			

Patient's signature		Date

Additional space for Comments:

APPENDIX VIII: TABLE OF TAGSNPS FOR A171601 STUDY

GENE	dbSNP rs id
CCND1	rs7177
	rs9344
	rs678653
CCND2	rs1049606
	rs3217805
	rs3217827
	rs3217869
	rs3217901
	rs3217907
	rs3217916
	rs3217936
	rs12299509
	rs3217840
	rs3217882
	rs3217926
CCND3	rs9529
	rs4607417
	rs4714554
	rs4714556
	rs7774393
	rs9369324
	rs9369325
	rs7753265
	rs1051130
	rs13340461
	rs4415146
	rs4560643
	rs4711703
CCNE1	rs1406
	rs997669
CDK2	rs2069408

GENE	dbSNP rs id
CDKN2A	rs2811710
	rs3218020
	rs3731239
CDKN2B	rs1063192
	rs3217992
	rs545226
	rs573687
	rs10811640
CDKN2C	rs12855
	rs3176459
CDKN2D	rs17677316
	rs3218222
CYP3A4	rs2246709
CYP3A5	rs4646450
	rs15524
RB1	rs9568036
	rs198584
SULT2A1	rs296365
	rs7508610
	rs296364
	rs2547238
	rs2932766
CYP19A1	rs2445761
	rs1062033
	rs2470152
	rs10519297
	rs1004983
	rs10459592
	rs12591359
	rs7172156
	rs3751592

CDK4	rs2072052			rs12592697
	rs2270777		***ESR1***	rs2982712
CDK6	rs1005346			rs2077647
	rs191777			rs3798577
	rs2079147			rs1643821
	rs42038			rs3020363
	rs42039			rs9340835
CDKN1A	rs2395655			rs532010
	rs3176336			rs11155820
CDKN1B	rs34329			rs3020370
	rs3759216			rs2982683
	rs7330			rs3020323
	rs34330		***CYP2A6***	rs1137115
	rs2066827			rs2316213
				rs56113850
				rs7250713

APPENDIX IX: PATIENT PHARMACOKINETIC QUESTIONNAIRE

Note: This form is required to be completed at all blood draw time points associated with the pharmacokinetic substudy (A171601-PP1).

On pre-study treatment visit (baseline), Cycle 1 Day 15 and Cycle 2 Day 15, this form is to be administered by a nurse/CRP, completed by the patient, and entered into Rave by site staff.

For baseline visit: The patient may indicate N/A for the questions that are not applicable.

Note: study medication should ONLY be taken on the day of the clinic visit after providing the PK blood sample.

Patient Initials: _____

Patient ID #: _____

Study #: _____

Cycle #: _____

Day #: _____

Date: _____

The following question refers to the day before yesterday (2 days ago):

What time did you take your oral study medication (palbociclib)? __ __:__ __ AM / PM

What dose of oral study medication (palbociclib) did you take on the day before yesterday ------ mg

The following question refers to yesterday (1 day ago):

What time did you take your oral study medication (palbociclib)? __ __:__ __ AM / PM

What dose of oral study medication (palbociclib) did you take yesterday ------ mg

The following question refers to today (THIS ONLY APPLIES IF YOU HAVE TAKEN YOUR STUDY MEDICATION BEFORE BEING SEEN IN THE CLINIC TODAY):

What time did you take your study medication (palbociclib)? __ __:__ __ AM / PM

What dose of oral study medication (palbociclib) did you take today? -------- mg

List concomitant medications patient is taking at baseline study visit ONLY: