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, HER2 negative metastatic breast cancer See 3.2.1
Measurable disease or non-measurable disease See 3.2.2
Planning to begin endocrine therapy for metastatic disease. One prior line of endocrine therapy/chemotherapy for metastatic disease is allowed. 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) See 3.2.5
No untreated brain metastases See 3.2.6
No second malignancies other than non-melanoma skin cancers or cervical carcinoma in situ See 3.2.7
No active infection requiring treatment with antibiotics See 3.2.8
Patients must be able to swallow and retain oral medication See 3.2.9
Patient Age: ≥ 70 years See 3.2.10
Patients must be able to read and comprehend English or Spanish See 3.2.11

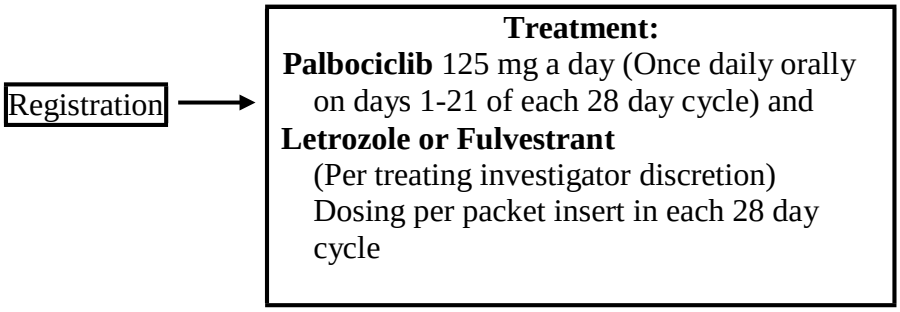
Required Initial Laboratory Values

ANC	≥ 1500/mm^3
Platelet count:	≥ 100,000/mm^3
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.

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.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.
- 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, 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 endocrine therapy for metastatic disease.** One prior line of endocrine therapy or chemotherapy for metastatic disease is allowed.

___ **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) 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 second malignancies other than non-melanoma skin cancers or cervical carcinoma in situ**

___ **3.2.8 No active infection requiring treatment with antibiotics.**

___ **3.2.9 Patients must be able to swallow and retain oral medication.**

___ **3.2.10 Patient Age: ≥ 70 years**

___ **3.2.11 Patients must be able to read and comprehend English or Spanish.**

___ **3.2.12 Required Initial Laboratory Values:**

Absolute neutrophil count (ANC)	≥ 1500/mm3 (1.5 x 109/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