|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Period** | **SCR** | **SCR** | **TRT** | | | | | | **EOT** | **FU** | | **Comments** |
| **Visit/Cycle** | **Tissue SCR** | **Cycle 1** | | **Cycle 2** | | **Cycle 3** | **Cycle 4** | **0** | **XD-FU** | **LTSFU** |
| **Day** | **-28 to -1** | **1** | **15** | **1** | **15** | **1** | **1** |
| **Window days** | **±2** | **±2** | **±2** | **±2** | **±7** | **±7** |
| **Eligibility Assessments** | | | | | | | | | | | | |
| Main ICF |  |  |  |  |  |  |  |  |  |  |  | SCR\*True-Is Biosample screening informed Consent to be obtained?: True |
| Eligibility Assessment | X | X |  |  |  |  |  |  |  |  |  |  |
| Demographics |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical History | X | X |  |  |  |  |  |  |  |  |  |  |
| **Safety Assessments** | | | | | | | | | | | | |
| Height | X | X | X |  | X |  | X | X | X |  |  | A full physical examination including an examination of all major body systems and breasts, height (at screening  only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. |
| Weight |  |  | X |  | X |  | X | X | X |  |  | A full physical examination including an examination of all major body systems and breasts, height (at screening  only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. |
| Physical Exam |  |  | X |  | X |  | X | X | X |  |  | A full physical examination including an examination of all major body systems and breasts, height (at screening  only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. |
| Vital Signs | X | X | X |  | X |  | X | X | X |  |  | A full physical examination including an examination of all major body systems and breasts, height (at screening  only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. |
| 12-lead ECG | X | X |  |  |  |  |  |  |  |  |  | SCR\*True-Required ECGs are: : Local  SCR\*True-Required ECGs, are done in triplicate for all timepoints or only at screening(and if abnormality noted)?: Yes  SCR\*True-When is the 12-lead ECG done for screening?: [28, 'Randomization']  SCR\*True-SOC scans allowed?(if taken before ICF): No |
| ECHO/MUGA |  |  |  |  |  |  |  |  |  |  |  |  |
| ECOG PS |  |  | X |  | X |  | X | X | X |  |  |  |
| Ophthalmologic Assessments | X | X |  |  |  |  |  | X | X |  |  | SCR\*True-Is Ophthalmologic Assessments done for screening?: Visual Acuity Testing |
| **Adverse Events** | | | | | | | | | | | | |
| AEs/SAEs | X | X | X | X | X | X | X | X | X | X | X | SCR\*True-Specify: Standard |
| **Medications, Nondrug Therapies, and Radiotherapy** | | | | | | | | | | | | |
| Prior/Concomitant therapies |  |  |  |  |  |  |  |  | X |  |  | SCR-Timing for screening?: [28, 'Randomization'] |
| Subsequent Anti-Cancer Treatment |  |  |  |  |  |  |  |  |  |  |  |  |
| **Laboratory Assessments** | | | | | | | | | | | | |
| Hematology & Chemistry |  |  | X | X | X | X | X | X | X |  |  | SCR-Select an option: Local Testing  SCR-Select an option: False |
| Coagulation |  |  |  |  |  |  |  |  |  |  |  | SCR-Select an option: False |
| Troponin |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinalysis |  |  |  |  |  |  |  |  |  |  |  | SCR-Select an option: False |
| Pregnancy Test | X | X |  |  |  |  |  |  |  |  |  | SCR\*True-Timing for screening?: [28, 'Randomization'] |
| HBV and HCV Test |  |  |  |  |  |  |  |  |  |  |  |  |
| HIV Test |  |  |  |  |  |  |  |  |  |  |  |  |
| Additional Safety Tests |  |  |  |  |  |  |  |  |  |  |  |  |
| **PK / ADA Assessments** | | | | | | | | | | | | |
| Blood for PK | X | X |  |  |  |  |  |  |  |  |  | SCR\*True-Will multiple drugs be tested for PK?: No  SCR\*True-Sample type for PK: Plasma  SCR\*True-Collected from: : Other |
| Blood for ADA |  |  |  |  |  |  |  |  |  | X | X |  |
| **Biomarker Assessments** | | | | | | | | | | | | |
| Archival Tumor |  |  |  |  |  |  |  |  |  |  |  |  |
| Newly Obtained Tumor Biopsy |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood sample for ctDNA/cfDNA |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood sample for WES/WGS control |  |  |  |  |  |  |  |  |  |  |  |  |
| Pharmacogenetics (Inherited Genetic Analysis) Sample |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood for biomarker analysis |  |  |  |  |  |  |  |  |  |  |  | TRT\_Cycle 1-Specify Window for collection: False |
| Other biomarker analysis |  |  |  |  |  |  |  |  |  |  |  | SCR-Select an option: False |
| **Efficacy Assessments** | | | | | | | | | | | | |
| Radiographic Tumor Assessment | X | X |  |  |  |  |  |  |  |  |  | SCR\*True-Include bone scan if history or suspicion of bone metastasis?: True |
| CT/MRI of Brain |  |  |  |  |  |  |  |  |  |  |  | SCR-Screening mandatory for: : All Subjects |
| Survival FU |  |  |  |  |  |  |  |  |  |  |  | FU-Timing for Follow-Up: : At least every Months  FU-Timing for Follow-Up: : False |
| **HEOR Assessments** | | | | | | | | | | | | |
| EQ-5D-5L EORTC QLQ-C30 |  |  | X |  | X |  | X | X | X |  |  |  |
| Healthcare Resource Utilization |  |  |  |  |  |  |  |  |  |  |  |  |
| **Trial Interventions** | | | | | | | | | | | | |
| Trial Intervention |  |  | X |  | X |  | X | X |  |  |  | Palbociclib  SCR-Enter investigational compound name: : Palbociclib |
| Comparator/Combination Partner |  |  | X | X | X |  | X | X |  |  |  | SCR-Administered By: : Not Applicable |

a. Active Treatment Phase: Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. No time window is to be considered for treatment schedule of palbociclib/placebo. One cycle consists of 28 days. A cycle could be longer than 28 days if persistent toxicity delays initiation of the subsequent cycle. Day 1 of any cycle visit should coincide with the day the palbociclib/placebo treatment begins. If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (+/-2 days allowed according to the protocol visit time windows). Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). The active treatment phase isongoing as long as the patient is receiving both study drugs (ie, palbociclib/placebo and fulvestrant) or fulvestrant alone.

b. Cycle 1/Day 1: Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.

c. End of Treatment/Withdrawal: Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study.

d. Post Treatment Follow-up: Patients who discontinue study treatment should be contacted 28 calendar days (+/- 7 days) after discontinuation of study treatment (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. This follow-up should occur 28 calendar days (+/- 7 days) regardless of any new anti-cancer therapy that may have started. Telephone contact is

acceptable. Follow-up visits to assess survival status will be conducted every 3 months going forward after approval of Amendment 3. See table footnote s (Survival Follow-up) below.

e. Informed Consent: Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Screening Section).

f. Medical/Oncological History: To include information on prior anticancer treatments.

g. Baseline Signs/Symptoms: Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

h. Physical Examination/Vital signs: A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. Physical examinations will be carried out at Screening, Day 1 of every cycle and the End of Treatment/Withdrawal visit.