ACCRU D0819C00003
A Phase III, Open Label, Randomized, Controlled, Multi-Centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy versus Physician’s Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline BRCA1/2 Mutations

FAST FACTS

Drug Company Supplied: Oral Olaparib

PATIENT SELECTION CRITERIA
Patients with unknown BRCA mutation status who are being considered for this trial should be identified early so that the appropriate BRCA mutation screening procedures can be put in place in a timely manner. These patients must fulfil all of the criteria marked with an asterisk * below prior to BRCA mutation testing being carried out.

Inclusion criteria
1. *Provision of informed consent prior to any study specific procedures
2. *Patients must be male or female ≥18 years of age
3. *Histologically or cytologically confirmed breast cancer with evidence of metastatic disease
4. Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) (See Section 3.1)
5. *Patients must have received treatment with an anthracycline (e.g. doxorubicin, epirubicin) unless contraindicated and a taxane (e.g. paclitaxel, docetaxel) in either an adjuvant or metastatic setting
6. *Patients who have received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer are eligible provided there has been no evidence of disease progression during the platinum chemotherapy
7. Patients who have received platinum for a prior cancer or as adjuvant/neoadjuvant treatment for breast cancer are eligible provided at least 12 months have elapsed between the last dose of platinum-based treatment and randomisation.
8. Patients with ER and/or PR-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic), or have disease that the physician believes to be inappropriate for endocrine therapy
9. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by CT (MRI where CT is contraindicated) and is suitable for repeated assessment as per RECIST 1.1
10. Normal organ and bone marrow function measured within 28 days prior to study treatment as defined below:
   • Hemoglobin ≥ 10.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days
   • Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   • Platelet count ≥ 100 x 10^9/L
   • Total bilirubin ≤ 1.5 x institutional upper limit of normal
   • AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN
   • Serum or plasma creatinine ≤ 1.5 x institutional upper limit of normal (ULN)
11. *ECOG performance status 0-1 within 21 days of randomization
12. *Postmenopausal or hysterectomized; women of childbearing potential are eligible with a negative urine or serum pregnancy test documenting evidence of non-childbearing status
   Postmenopausal is defined as:
   • Age ≥ 60 yrs
- Age < 60 and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
- Luteinizing hormone (LH), follicle stimulating hormone (FSH) and plasma oestriadi levels in the postmenopausal range for women under 60 years of age
- radiation-induced oophorectomy with last menses >1 year ago
- or surgical sterilisation (bilateral oophorectomy or hysterectomy)

13. *Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations

14. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour if available

For inclusion in:
- a) the optional exploratory genetic research and/or
- b) the optional tumour biopsy research,

Patients must fulfil the following criteria:
- Provision of informed consent for genetic research
- Provision of informed consent for tumour biopsy research

If a patient declines to participate in the optional exploratory genetic research or the optional tumour biopsy research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

**Exclusion criteria**

1. *Involvement in the planning and/or conduct of the study (AstraZeneca staff/BCA staff and/or staff at the study site)

2. **BRCA1** and/or **BRCA2** mutations that are considered to be non detrimental (e.g., “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favour polymorphism” or “benign polymorphism” etc.)

3. Cytotoxic chemotherapy or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. Endocrine therapy must have been discontinued 7 or more days before Cycle 1 Day 1. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to study treatment

4. *Patients with HER2-positive disease (3+ by IHC or ISH amplified ≥ 2.0)

5. *Previous randomization in the present study

6. Exposure to an investigational product within 30 days or 5 half lives (whichever is longer) prior to randomization

7. *Any previous treatment with a PARP inhibitor, including olaparib

8. *Patients with second primary cancer, **Exceptions**: adequately treated nonmelanoma skin cancer, curatively treated in-situ cancer of the cervix, DCIS, stage 1 grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years prior to study entry

9. Resting ECG with QTc > 470 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec

10. *Patients cannot have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease. Prior treatments with hormonal therapy and non-hormonal targeted therapy are allowed and not counted as a prior line of cytotoxic chemotherapy. For the purposes of this protocol, the combination of an aromatase inhibitor and everolimus is not considered cytotoxic chemotherapy

11. *Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further detail refer to Appendix I
12. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy

13. *Patients with myelodysplastic syndrome/treatment related acute myeloid leukaemia

14. Major surgery within 2 weeks of starting study treatment: patients must have recovered from any major surgery

15. *Immunocompromised patients, e.g., patients who are known to be serologically positive for HIV

16. *Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive bilateral lung disease on High Resolution Computed Tomography scan or any psychiatric disorder that would limit ability to comply with study procedures, and any other medical condition that, in the opinion of the investigator, places the patient at unacceptable risk of toxicity

17. *Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No clinical evidence of progression since completion of CNS-directed therapy. Minimum of 2 weeks between completion of radiotherapy and cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing requirement for > 10mg of prednisone per day or an equivalent dose of other corticosteroid

18. *Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication

19. Pregnant or breast feeding women

20. *Previous allogeneic bone marrow transplant

21. *Patients with a known hypersensitivity to olaparib or any of the excipients of the product

22. *Whole blood transfusions in the last 120 days prior to enrolment to the study which may interfere with gBRCA testing

**TREATMENT**

- **Experimental: Olaparib**
  Patients will be administered olaparib orally twice daily (bid) at 300 mg. Two (2) x 150 mg olaparib tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water.

- **Active Comparator: Physician’s choice chemotherapy**
  Capecitabine 2500 mg/m2 d1-14 q 21, or Vinorelbine 30 mg/m2 d1,8 q 21, or Eribulin 1.4 mg/m2 d1,8 q 21

**PRE-STUDY PARAMETERS** (refer to Table 1 for details)

- Medical and surgical history, physical examination and vitals
- Adverse event assessment
- Concomitant medications including blood transfusions
- Urinalysis and pregnancy test
- CBC and CMP
- Tumor assessments using RECIST 1.1
- Electrocardiogram
- Mandatory blood samples BRCA status
- Mandatory archived tissue sample and blood samples for research
- Optional tumor biopsies at screening and progression
- EORTC QLQ-C30, CTSQ-16 and PRO-CTCAE