Background

- Triple negative breast cancer (TNBC)
  - Constitutes 10-15% of breast cancer diagnoses; associated with poor prognosis
  - No targeted treatments currently available
  - 40-60% of sporadic TNBC display defective homologous recombination (HR) DNA repair (low RAD51 score)\(^1,3\)
  - Proportion of sporadic TNBC have reduced BRCA1 expression\(^4\) or increased methylation of BRCA1 promoter region\(^5\)

- PARP inhibitors:
  - Known to specifically target cancers defective in HR
  - Demonstrated response observed in breast and ovarian cancers associated with germline BRCA 1/2 mutations\(^6\)

- Rucaparib:
  - Potent, small molecule inhibitor of PARP 1, 2 and 3 with activity as a single agent detectable in both in BRCA1 and BRCA2 mutation related cancers
  - Response also seen in BRCA wild-type cancers\(^7\)

Trial Aims and Design Rationale

- RIO aims to assess activity of rucaparib in treatment naïve sporadic TNBC population.

- **Principal aim** of RIO is to determine the proportion of patients with sporadic TNBC who display sensitivity to rucaparib using Ki67 as a surrogate marker of activity and to characterise biomarkers predictive of response

- **RIO is a Window of Opportunity** study:
  - Trial treatment given during period between diagnosis and commencing standard care (surgery or neo/adjuvant chemotherapy)
  - Minimises impact on patient care pathways
  - Flexible treatment duration (12-14 days) reduces potential delays in scheduling normal patient care treatments

- Biological samples – Research sample collection is integral to success of the trial
  - Core biopsies (1 x FFPE 1x RNA Later) and research bloods collected pre and post treatment
  - To maximise successful collection and minimise additional biopsy collection from patients, two pathway options are available (see Trial Schema)

Trial Schema

- **RIO is a single group, open-label, multi-centre phase II trial conducted within the UK**
  - 81 patients with primary, sporadic TNBC will be enrolled into this study
  - Additionally ≤ 20 pts with known germline BRCA 1/2 mutations will also be eligible for participation
  - Tumour size (by ultrasound) ≥ 1.5cm OR < 1.5cm with confirmed axillary lymph node metastases
  - Interim analyses
    - Futility analyses will be performed at 20 and 41 evaluable patients

- **Patients with a new diagnosis of either a sporadic triple negative breast cancer or a BRCA 1/2 related breast cancer who would otherwise proceed with routine surgery or neoadjuvant chemotherapy**

- **Patients presenting with underprogressed breast lump**

- **Patients with a new diagnosis of either a sporadic triple negative breast cancer or a BRCA 1/2 related breast cancer who would otherwise proceed with routine surgery or neoadjuvant chemotherapy**

- **Pathway 1:**
  - BRCA1 dysfunction in sporadic basal type cancers

- **Pathway 2:**
  - BRCA 1 and/or 2 mutation related cancers

- **Pathway 3:**
  - Baseline blood sample (PBMCs or FFPE from breast tumour) or breast tumour

- **Study specific informed consent**

- **Baseline visit**
  - Research blood samples (x 3 FFPE, x 1 Cell Free DNA (CFD)) from all patients

- **All patients receive 12-14 days rucaparib treatment prior to surgery/neoadjuvant chemotherapy (6, 8, 10)**

- **Patients proceeding to surgery as part of standard care**

- **Preoperative**
  - (Day 0-4 of rucaparib, baseline non-blood samples, research on blood samples)

- **Day 12-14 WKT**
  - Surgery
  - (During surgery, serum採集 in MIT, FFPE in Pathnet)

- **Total trial cost** (all days post rucaparib)

- **Pathway 1**:
  - (anticipated implementation Nov 2016)

- **Pathway 2**:
  - (anticipate trial completion Apr 2017)

- **Pathway 3**:
  - (anticipate trial completion Oct 2017)

Trial Endpoints

- **Primary Endpoint:**
  - Ki67 response between baseline and end of treatment (EOT). Response defined as ≥ 50% decrease in Ki67 from baseline

- **Secondary Endpoints:**
  - Association between baseline biomarkers and Ki67 response to rucaparib
  - BRCA1 methylation status
  - Genomic predictor of HR deficiency
  - Apoptosis induction following rucaparib treatment in sporadic TNBC patients as assessed by cleaved PARP analysis

- **Association between sporadic TNBC and evidence of defects in HR DNA repair (assessed by RAD51 fold formation)**

- **Association of biomarkers with RAD51 score at end of treatment**

- **Exploratory Endpoints:**
  - Proportion of patients with germline BRCA 1 and/or 2 mutation related cancers with:
    - Ki67 response to rucaparib
    - Reduced RAD51 score
    - Increased apoptosis induction
  - Change in circulating tumour DNA between baseline and EOT as surrogate for efficacy of rucaparib and association between change in ctDNA levels and biomarkers
  - Change in tumour cellularity between baseline and EOT

Current Progress

- **RIO opened for recruitment in June 2015; 28 patients have been recruited to date. 9 centres from currently open, 6 of whom have recruited at least one patient.**

- **First interim analysis has been completed. No safety concerns were raised and trial continuation was supported by the IDMC**

- **Protocol amendments are being implemented to boost recruitment:**
  - Reduction of tumour size from ≥2cm to ≥1.5cm (implemented August 2016)
  - Provision for use of diagnostic block if baseline pre-treatment sample unavailable (anticipated implementation Nov 2016)

- **It is anticipated that the successful completion of RIO will inform the design of larger scale efficacy studies in rucaparib-sensitive sporadic TNBC patient subgroups**