RIO: Window study of the PARP inhibitor rucaparib in patients with primary triple negative or BRCA1/2 related breast cancer

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Background

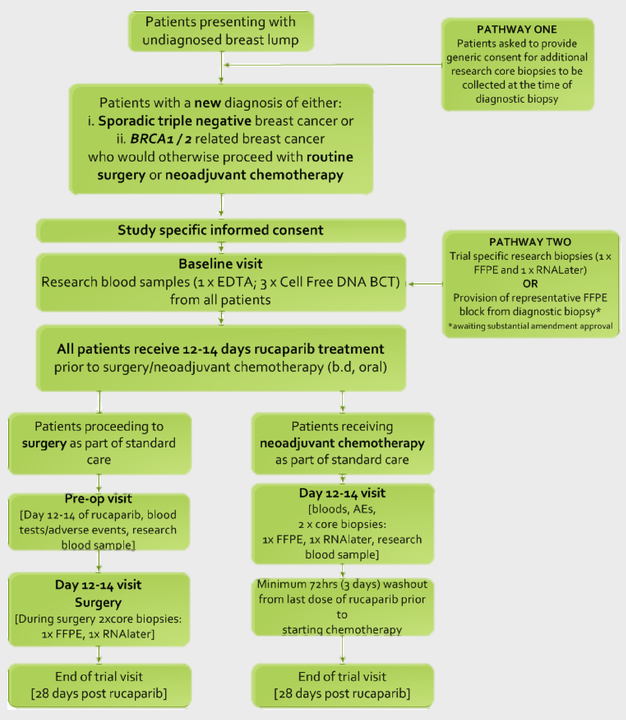
- **Triple negative breast cancer** (**TNBC**)
  - Constitutes 10-15% of breast cancer diagnoses; associated with poor prognosis[1]
  - No targeted treatments currently available
  - 40-60% of sporadic TNBCs display defective homologous recombination (HR) DNA repair (low RAD51 score)[2,3]
  - Proportion 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 germline and sporadic *BRCA1* or *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 neoadjuvant 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 analysis will be performed at 20 and 41 evaluable patients



Trial Endpoints

Primary Endpoint:

- Ki67 response between baseline and end of treatment (EoT). Response defined as ≥ 50% decrease in Ki67 from baseline

Secondary Endpoints:

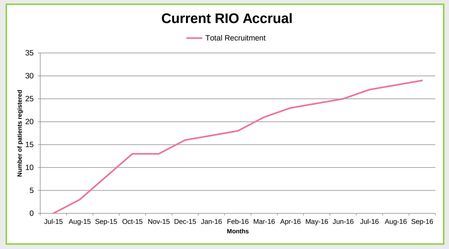
- Association between baseline biomarkers and Ki67 response to rucaparib
  - *BRCA1* methylation status
  - Genomic predictor of HR deficiency
- Apoptosis induction following rucaparib treatment in sporadic TNBC patients as assessed by cleaved PARP analysis
- Association between sporadic TNBC and evidence of defects in HR DNA repair (assessed by RAD51 foci 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 are 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

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