Intermittent PARP Inhibitor in Recurrent Ovarian Cancer (IPIROC)

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Trial setting: Recurrent ovarian cancer Trial Model: Academic (A)
Trial status – New Concept development stage

Study Design: Translational proof of concept leading to Phase 2 RCT (IPIROC series)
Peer Review: CRUK-DBT(India) affordable approaches (global challenge) seed fund (awarded)

GCIG Groups: KolGo Trg (Kolkata Gynecology Oncology Trials and Translational research group, India)
(KolGo-PROVAR-002). More suited for LMICs.
(GCIG mentors: McNeish/Bookman/Oza) - (Discussed with UK and Canadian group members).

Sponsor(s): KolGo Trg/ Chittaranjan National Cancer Institute (CNCI) Kolkata
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PARP inhibitors in LMICs- Rationale for the study

Biological optimal dose **may be different from** **Maximally Tolerated Dose (MTD).** Current approved dosing is largely based on MTD derived from small phase I and phase II trials based on toxicity assessment within the first 28 days (cycle 1 MTD). However, PARP inhibitors are frequently administered for many months, and patients have required dose and schedule modifications to manage serious toxicities, including fatigue, anorexia, and low blood counts (neutropenia, thrombocytopenia, anaemia) with impact on **quality of life**. **In India (Eastern) ∽30% women have germline BRCA mutations and younger- median age 51 years; Majority of women are anaemic and body weight <70 Kg**

Early pre-clinical and clinical data with these agents failed to provide clear guidance regarding dose, but suggested that inhibition of PARP could be achieved with lower dosing, and **that the biologic impact of single-dose PARP inhibitor could persist for more than one day**.

Not affordable- In LMICs, majority of women/governments and even insurances will not be able to afford targeted therapy (PARPi). Financial drain (catastrophe) often limits majority of chemotherapy based treatment options at recurrence. Maintenance PARPi in frontline therapy would be largely impossible and leave a lot of women/ family members and doctors feeling helpless and disadvantaged due to post code. There are ethical issues for causing emotional harm.

Academic study- Pharmaceutical sponsors may be reluctant to investigate alternative reduced dose schedules, based on **pharmacoeconomic concerns.** However, optimized dosing could have an important clinical safety and financial impact that would benefit our patients. Even in high resource settings- can it be a **cost effective alternative** in a select subgroup of patients without compromising the survival and thereby reserving the PARP for recurrence (less resistance?). Also, it may be highly relevant in the **current economic climate.**

Patients with **recurrent platinum-sensitive** ovarian cancer have incurable disease, but a proportion of these patients will respond to treatment with a PARP inhibitor for a period of time, usually less than 10 months. **The event rate for recurrent disease is 100% and the overall response rate following treatment with a PARP inhibitor is approximately 30%.** Therefore, this would be an appealing cohort of patients to study.

Origin of proposal: Preclinical data from Newcastle DNA repair group (Prof Nicola Curtin) BJC, 2014; Cancers 2020

A

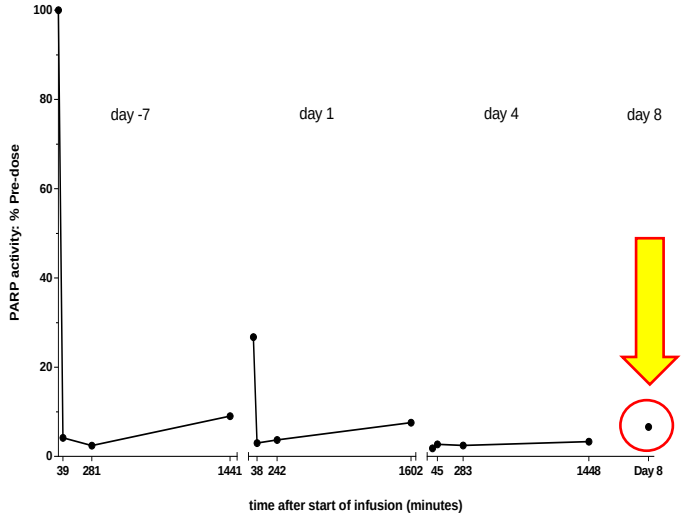
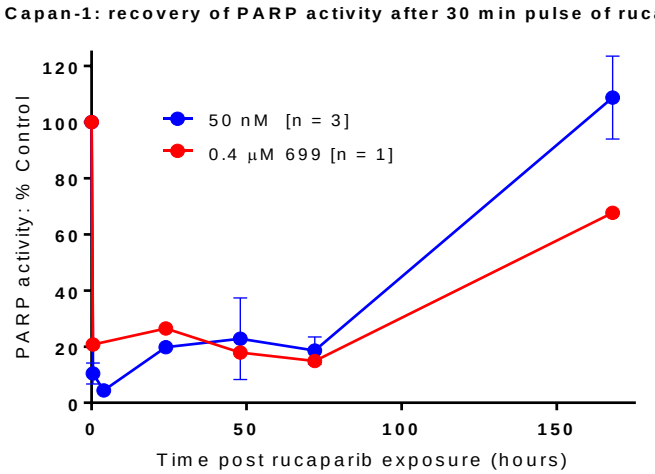


Figure 1. *The first in human clinical trial, a Phase I trial of Rubraca®(then called AG 014699)in combination with temozolomide, was conducted in 2003 in Newcastle. As part of this trial we measured PARP activity in peripheral blood mononuclear cells. We noted profound suppression of PARP activity that persisted for >24 h, and was also measurable 72 h after the last i.v. dose of 12 mg/m^2 (equivalent to approx. 60 mg oral dose): PARP activity in lymphocytes from a patient receiving rucaparib i.v. 12 mg/m2 (equivalent to approx. 60 mg oral dose). Note PARP activity suppressed Day 8 after final dose on day 5.*[1]

B



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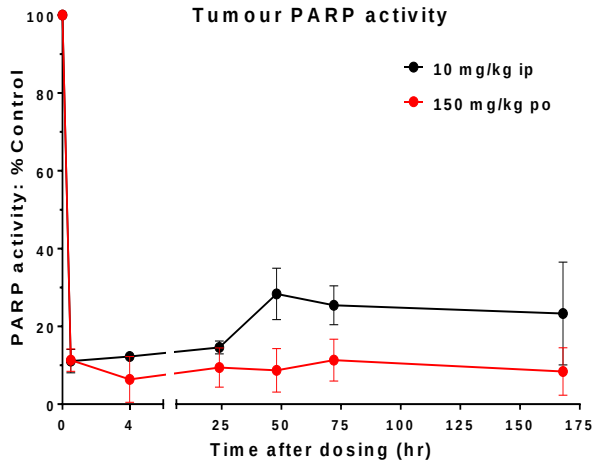
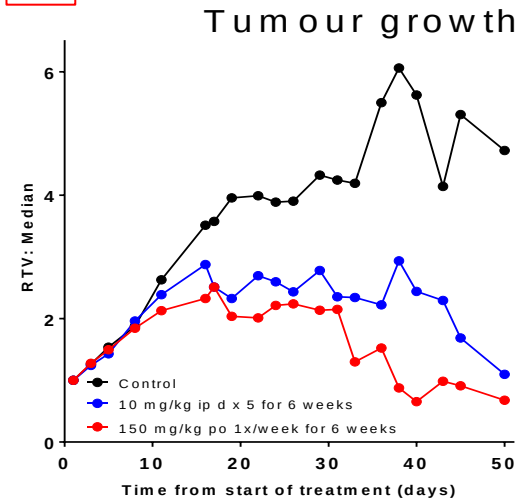


The durability of PARP inhibition A) Patients B) in Capan-1 cells after a 30 min pulse followed by incubation in fresh medium and C) in Capan-1 tumour xenografts following a single oral dose of 150 mg/kg (equivalent to 50 mg/kg i.p) or 10 mg/kg i.p.. D) The antitumour activity of rucaparib at 150 mg/kg (equivalent to 50 mg/kg i.p due to 30% oral bioavailability) weekly for 6 weeks or 10 mg/kg i.p. dailyx5/week for 6 weeks

D



Single dose of rucaparib showed durable parp inhibition beyond 72hrs

UKIERI project: Discussions between Curtin & Mukhopadhyay since 2018 February after her presentation in Kolkata explaining an example of science and serendipity- Idea and concept for a potential clinical trial in LMIC

Summary of proposed study schema: IPIROC series

- **IPIROC # 1: Translational proof of concept (cell lines/ovarian cancer patient samples and in vivo work)- ongoing work (since 2018) – to find out which other PARPi also have durable inhibition after single dose and in ovarian IP models**

(Funding: UKIERI; Mukhopadhyay/Curtin/Drew/McNeish)

- **Phase 0 study in UK and India (single dose PARPi → measure duration of PARP inhibition in PBMC and ascites (PD immunoblot assay)- find out the optimal duration of inhibition/intervals**

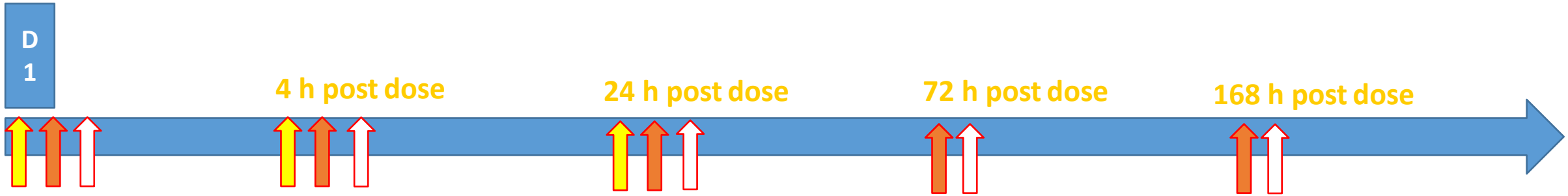
(Funding: CRUK-DBT India and UKIERI: Mukhopadhyay/Curtin/Drew/McNeish)

Phase 0 translational proposed design and PD/PK blood and ascitic fluid sampling

(24 h, 72 h and 168 h time points have +/-4 hour window)

Target patient population: recurrent HGSOC, post PARPi therapeutic treatment, able to swallow a single dose of PARPi X, PS=0-3, able to comply with the protocol schedule visits for additional blood sampling

Single oral dose PARP inhibitor X given at time zero



Pre-dose of PARPi X:

1. Whole blood (EDTA) 10 ml for PBL extraction for baseline PARP activity (PD) Red
2. Blood sample for PK PARPi 5 ml (PK) white
3. If patient undergoing ascitic drain pre-dose ascites sample for baseline PARP activity (PD) Yellow

1. Whole blood 10 ml for PBL extraction for PARP activity (PD)
2. Blood sample PK
3. If patient undergoing ascitic drain fresh ascites sample (insert volume) for PD/PK drug levels

1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample PK
3. If patient undergoing ascitic drain fresh ascites sample (insert volume) for PD/PK drug levels prior to drain removal

1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample for PK

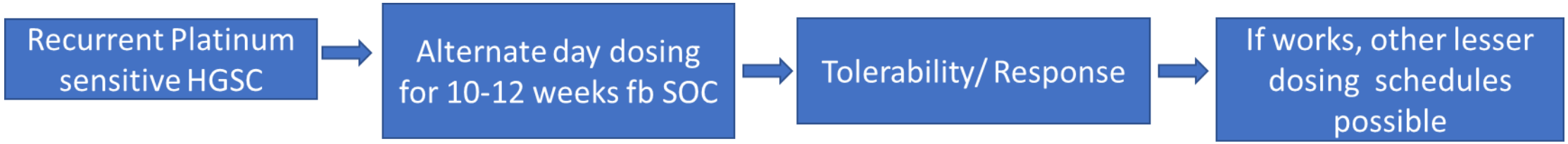
1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample for PK

Drew, Curtin, Mukhopadhyay

Summary of proposed study schema: IPIROC series

IPIROC #2. Pragmatic approach in India using available PARPi (Exploratory/Window of opportunity study before SOC) [Proposed start 2021]

(Designed by Michael Bookman and Amit Oza)

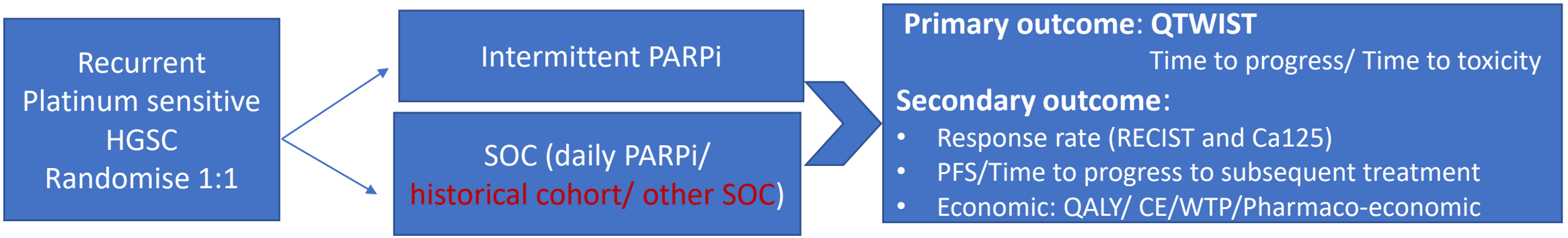


- **Non-randomized single arm exploratory study of 10-12 women with platinum sensitive recurrent (1st or 2nd) relapse (including BRCA germline mutations) to confirm that a modified schedule (alternative day dosing) has lower incidence of toxicity and avoids dose reduction or dose elimination within the first 12 weeks and translational end points (PARP inhibition by biopsy-optional).**
- **At end of treatment, patients will go on to standard treatment chemotherapy of physician's choice**
- **Tolerability – no of patients not requiring dose reduction/ elimination**
- **Efficacy will be measured by CA125 and/or radiological response (RECIST 1.1) and Pathological/PD wherever feasible (baseline versus post treatment)**
- **Follow up to continue for 12 months (? Include a historical control receiving standard of care treatment only)**
- **If this is successful, we can go for other lesser dose schedules in this format/ Phase 2 depending on funding.**

IPIROC #3. Phase II (development phase) [Planned accrual-2021/2022]

Proof of concept clinical trial for intermittent dosing PARPi with QOL-adjusted survival/toxicity/economic endpoints

- Once we confirm that the modified schedule(s) is well tolerated, we would begin a randomized phase II study using the available PARPi compared to the standard of care (SOC) [pragmatic approach].
- This will also depend on the results of IPIROC#1, in selecting the most appropriate PARPi and intervals and if that PARPi would be available in India by then. The SOC arm would ideally be a daily PARPi regime; however other options (SOC commonly used in India/LMICs **or** a historical/hypothetical cohort on daily PARPi) may need to be considered depending on **funding (academic/industry) available** and sample size (/design) will depend accordingly, adapting to various options.
- Primary study hypothesis: **QTWIST will be better in the experimental group (superiority design).** A direct comparison of response rates or PFS using a non-inferiority design would require larger number of patients (& resources)
- Cross over design; Duration of treatment: Time to progress



Translational: HRD status, PK/PD and pharmacogenomic studies, if feasible

IPIROC # X …Other lesser dosing schedules/ Frontline/maintenance/ any HRD cancers (basket)

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UKIERI UK-India Education and Research Initiative

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