Intermittent PARP Inhibitor Regimen in Ovarian Cancer (IPIROC)

Asima Mukhopadhyay

- **Trial setting**: Recurrent ovarian cancer Trial Model: Academic (A)

- **Study Design**: Translational proof of concept leading to Phase 2/3 studies (IPIROC series)
- **Peer Review**: CRUK-DBT(India) affordable approaches (global challenge) seed fund and ICMR extramural fund (awarded 2024)
- **GCIG Groups**: KolGo Trg (Kolkata Gynecology Oncology Trials and Translational research group, India (KolGo-PROVAR-002).
- (GCIG mentors: McNeish/Bookman/Oza) - Presented to other GCIG member groups
- **Sponsor(s)**: KolGo Trg
- **Presenter name and email**: Email: asima7@yahoo.co.in

Disclosure: Royalty payment from Newcastle University, UK for contribution towards development of Rucaparib (Clovis Oncology) → Donated for research capacity building in LMICs

KolGO-PROVAR #02: IPIROC

Intermittent PARP inhibitor regimen in Ovarian cancer: Proof of concept and a master protocol

- **Hypothesis**: **It is an acceptable alternative for optimal scheduling of Parp inhibitors**

  De-escalation study (esp. in women who can not tolerate/afford daily dosing)

  -Symptom benefit: MOREPARP (MOrbidity REduction with PARPi, physical and financial)
- **Mixed methodology research-** umbrella of studies (Preclinical /clinical): Triangulation of evidence
- **Low-cost, Pragmatic and/or novel study designs** using **KolGoTrg RCT approach** (rationalizing and reducing the cost of running randomised controlled trials in low resource setting) and implementation research – **EASE model**
- Patient involvement in research design and patient participatory model ensuring patient-centric outcome measures (**patient advocacy**)
- Multicentric and opportunity to participate in one /other components of the studies based on feasibility/ desirability of the site (**provider advocacy**)
- GCRN/OCRN & OCCC 6th consensus committee guidance for clinical research

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

A

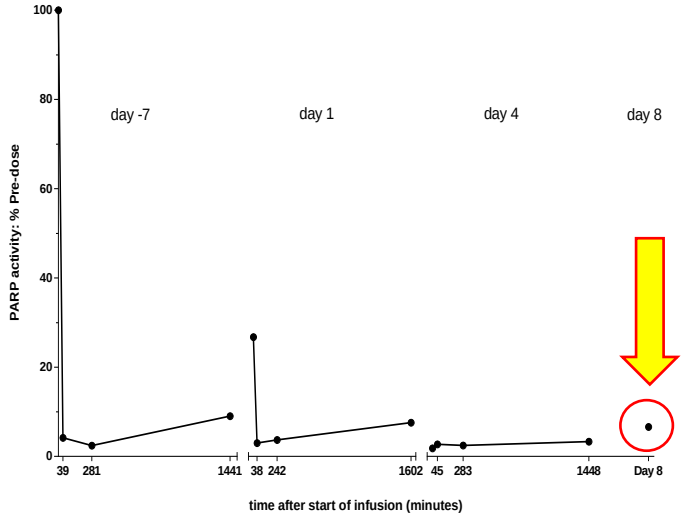
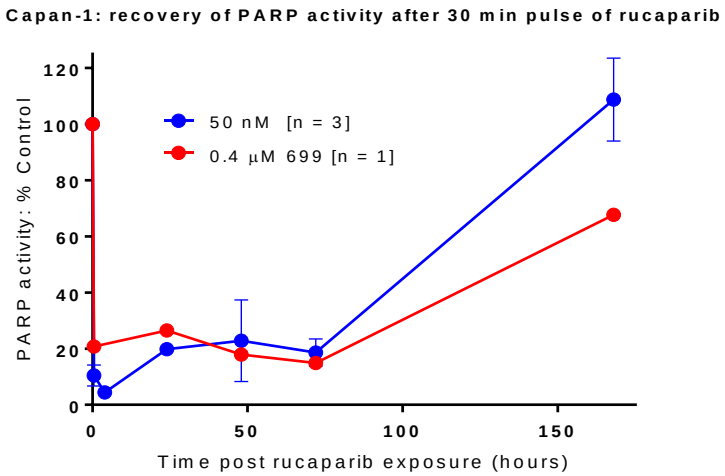


Figure 1. *The first in human clinical trial, a Phase I trial of Rubraca®(then called AG 014699)in combination with temozolomide, was conducted in 2003 in Newcastle. As part of this trial we measured PARP activity in peripheral blood mononuclear cells. We noted profound suppression of PARP activity that 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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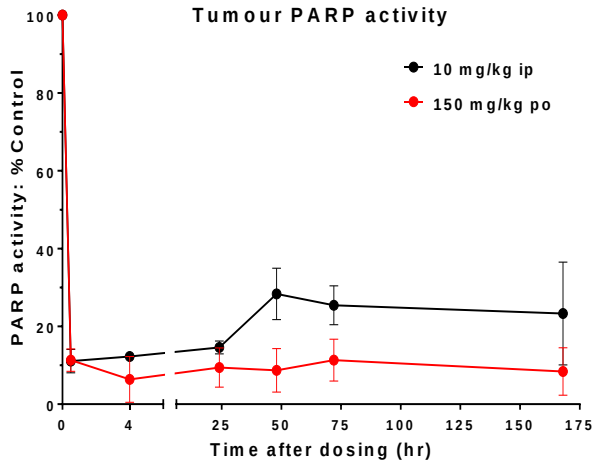
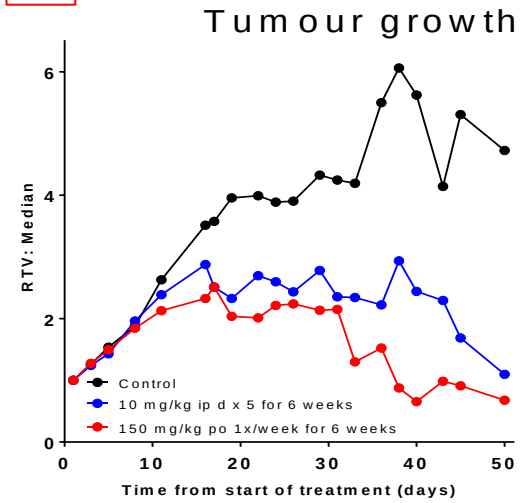


The durability of PARP inhibition A) Patients B) in Capan-1 cells after a 30 min pulse followed by incubation in fresh medium and C) in Capan-1 tumour xenografts following a single oral dose of 150 mg/kg (equivalent to 50 mg/kg i.p) or 10 mg/kg i.p.. D) The antitumour activity of rucaparib at 150 mg/kg (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 (PBMC, Clinical trial 2003; xenograft studies, 2014)

IPIROC # 1: Translational proof of concept – to find out which other PARPi also have durable inhibition after single dose and what should be the interval for intermittent dosing *(Funding: UKIERI; CRUK DBT 2020 Mukhopadhyay/Curtin/Drew)*

medical sciences forum

MDPI

Abstract

Differences in Durability of PARP Inhibition by PARP Inhibitors in Ovarian Cancer Cells †

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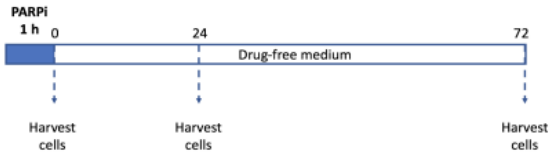
* Correspondence: hannah.smith2@newcastle.ac.uk
† Presented at the 1st International Electronic Conference on Cancers: Exploiting Cancer Vulnerability by Targeting the DNA Damage Response, 1–14 February 2021; Available online: https://iecc2021.sciforum.net/.

Abstract: Background: PARP inhibitors (PARPi) exploit defects in homologous recombination repair (HRR) to selectively kill tumour cells. Continuous PARP inhibition is required for cytotoxicity. PARPis rucaparib, olaparib, and niraparib have been approved for use in ovarian cancer on continuous schedules. Previous studies demonstrate prolonged PARP inhibition by rucaparib [1]. Aim: To determine if persistent PARP inhibition is a class effect. Methods: IGROV-1 (human ovarian cancer) cells were treated with 1 μM of rucaparib, olaparib, niraparib, talazoparib, or pamiparib for 1 h before drug was washed off and replaced with fresh media for 0, 1, 24, 48, or 72 h prior to harvesting. Cellular PARP activity was measured using a GCLP-validated assay [2] in comparison with untreated controls and where 1 μM inhibitor was added to the reaction. Results: rucaparib, olaparib, niraparib, talazoparib, and pamiparib each inhibited PARP activity in permeabilized cells > 99% when 1 μM was present during the reaction. After 2 h in drug-free medium, rucaparib-induced PARP inhibition was

Citation: Smith, H.L.;

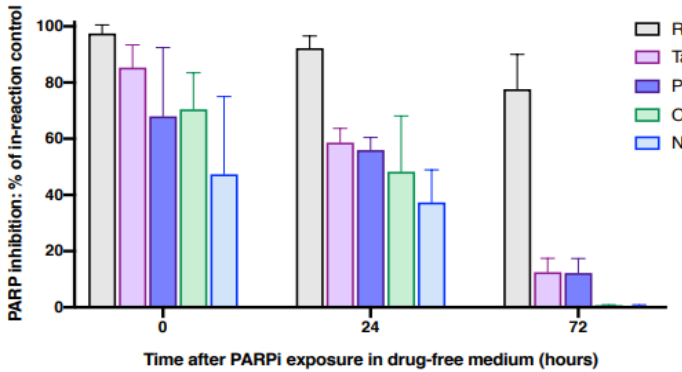
oligonucleotide to mimic DNA breaks and an excess of the substrate NAD+ [6]. The assay based on the following reaction:



IGROV-1 ovarian cancer cells were treated with 1 μM rucaparib, olaparib, niraparib, talazoparib or pamiparib for 1 hr before drug was washed off and replaced with fresh media. Cells were harvested and cellular PARP activity was measured and compared to untreated control and where 1 μM was added directly to permeabilised cells in the reaction.

Results

Rucaparib, olaparib, niraparib, pamiparib and talazoparib each inhibited PARP activity >99% in permeabilised cells with 1 μM added to the reaction.



- Rucaparib, olaparib, niraparib, talazoparib and pamiparib each inhibited PARP activity in permeabilised cells >99% when 1μM was present during the reaction.
- Only rucaparib maintained this level of inhibition in cells harvested immediately after exposure to PARPi, with the other inhibitors only inhibiting PARP 47-85%, suggesting failure to achieve adequate intracellular concentrations or wash-out during harvesting.

- Rucaparib is unique in its ability to cause persistent PARP inhibition compared to other PARPis and it is not a class effect.
- These data have important clinical implications for the different uses of PARPi: for single agent activity exploiting HRR defects durable PARP inhibition is required. In contrast, for combinations with cytotoxic agents causing DNA SSBs (e.g temozolomide, topotecan, radiotherapy) less durable PARPi may be less toxic.
- These data suggest that the current twice daily dosing approved for rucaparib treatment may not be necessary. Further studies are needed to determine whether less frequent dosing would have equivalent anticancer activity.

- After 24 h in drug-free medium rucaparib-induced PARP inhibition was maintained at 92.3 ± 4.3% but was much less with talazoparib (58.6 ±5.0%), pamiparib (56.0 ± 4.5%) olaparib (48.3 ± 19.8%) and niraparib (37.3 ± 11.6%)
- PARP inhibition declined with time but in rucaparib-treated cells was maintained for 72h in drug-free medium (77.7 ± 12.3%). This sustained PARP inhibition was not observed with the other PARPis. PARP inhibition was only 12.3 ± 5.2% and 12.5 ± 4.9% 72h after talazoparib and pamiparib, respectively, and undetectable with olaparib and niraparib.

Rucaparib showed the maximal durable response after single dosing and is not a class effect

Road Map to Safe and Well-Designed De-escalation Trials of Systemic Adjuvant Therapy for Solid Tumors

DOI: 10.1200/JCO.20.01382 *Journal of Clinical Oncology* 38, no. 34 (December 01, 2020) 4120-4129

Involving Patients in the Design and Conduct of De-escalation Trials

Risk Tolerance in context of Shared Decision-Making Process

- assess patients' view on risk benefit ratio
- determine maximum 'loss' patients are willing to accept
- ask about the most meaningful endpoint to the patient / willingness to pay

Selection of patient population

- consider feasibility survey with patients, nurses, doctors
- avoid broad eligibility resulting in too much heterogeneity in disease burden

Road Map to Safe and Well-Designed De-escalation Trials of Systemic Adjuvant Therapy for Solid Tumors

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Non-randomised studies

- Determine event rate in well matched controls treated with SOC in a recent time-period
- Only appropriate when expected event rate is relatively low
- Select a threshold for disease outcome under de-escalated therapy with a narrow confidence interval

Randomised studies

- Trials assessing shorter duration of therapy- favour late time of randomisation closer to point of divergence
- Substantial treatment non-adherence- per protocol analysis may be more appropriate

Road Map to Safe and Well-Designed De-escalation Trials of Systemic Adjuvant Therapy for Solid Tumors

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Selection of endpoints

- Use of intermediate end point with established individual patient-level surrogacy
- avoiding distant metastasis is very important for patients – DMFS,DMFI, RFI, RFS
- analyses treatment related deaths separately
- standardized PROM
- Non-inferiority vs superiority

Facilitating Patient- doctor communication and education

- explain de-escalated treatment benefits and short/long term risks
- explain aim of the study- reducing side effects or costs or both
- use videos/visual aids to explain complicated aspects of the trial

IPIROC master protocol (umbrella/platform of pre-clinical and clinical studies)- Combining a single protocol and start at separate time points- with separate end points and different centres willing to participate in different components

1.**Determination of SOC (methodological research) in resource adapted settings when prescribed SOC is not SOC**

- **Systematic review** on inclusivity of the prescribed SOC dosing for OC patients in LMICs
- **Survey- patient and provider**- University of Michigan & MRC Biostatistical unit, Cambridge University (India and IGCS training sites)
- **Willingness to pay survey (Cost benefit)**- India and UK (Newcastle University) – IGCS training sites
- **Registry on PARPi use in India to determine SOC (ICMR grant)**

2. Interventional studies:

- **Feasibility /exploratory study in treatment setting** – Intermittent single arm (CRUK DBT grant) for the exploratory cohort on 10-12 women with recurrent platinum sensitive OC for feasibility followed by extending the study to N=40 for DCR, tolerability and duration of response and translational endpoints (PK/PD/PG) (status: ongoing and will apply to DBT for extension)

- **Phase 2 RCT in platinum sensitive 1st recurrence maintenance setting after response to platinum, using adaptive trial design (non-inferiority signal and toxicity/QA adjusted/Pharmaco-economic/affordability endpoints and assessment) - ICMR grant received**

- Single arm prospective observational study for intermittent dosing **maintenance** rucaparib (patient/provider participatory model)

- Phase 2/3 RCT in frontline maintenance in HRD/ BRCA setting using adaptive trial design/ SMART/Basket (2-year PFS and other secondary endpoints)- will apply for separate funding

3. Methodological Research

- Implementation research project on de-escalation of PARPi study (EASE model)
- Novel adaptive trial designs (RAR/SMART) and translational - (PK/PK/PG guided scheduling) and prediction of non responders

Patient involvement in study design- (PPI toolkit): 2020-2021

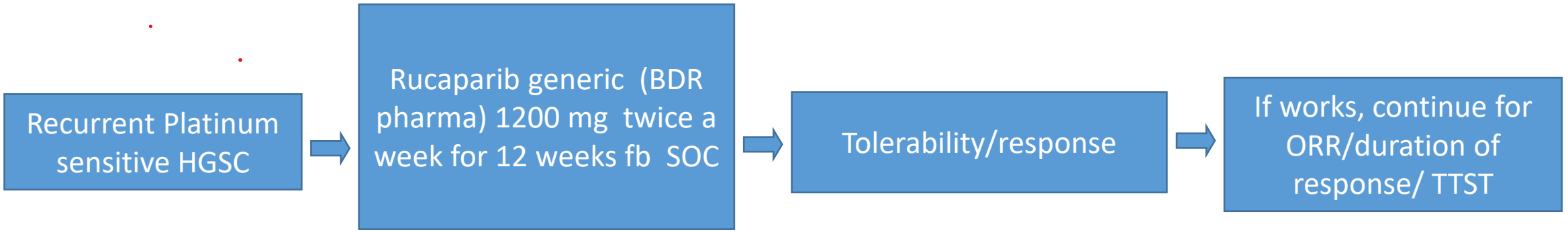
UKIERI
UK-India Education and Research Initiative

CANCER RESEARCH UK

Department of Biotechnology
Ministry of Science & Technology
Government of India

- Willingness to pay study
- Acceptance of detriment in efficacy versus affordability and toxicity/QOL
- Feasibility and scalability (Patient and provider)

IPIROC #2. Pragmatic approach using PARPi (Rucaparib generic) (Exploratory/ Feasibility) [2022- 2023]



Non-randomized single arm, open label exploratory study in women with platinum sensitive, recurrent HSGC to confirm that a modified schedule (bi-weekly dosing) has lower incidence of toxicity and avoids dose reduction /elimination within the first 12 weeks with acceptable disease control rate (DCR)/ORR and translational end points.

- **N=40 (If 20% Loss to follow up anticipated- n=50).** Bayes factor single arm binary model, Minimum number for applying stopping rule=10, cohort size=5.
- **Tolerability – no of patients not requiring dose reduction/ elimination; Toxicity (PARPi specific) and QOL (EQ-5D/ MOST)**
- **Efficacy- measured by CA125 and radiological response (RECIST 1.1) - 6 weeks and 12 weeks**
- **At the end of treatment, patients will go on to standard treatment of physician's choice/ patient preference**
- **Follow up to continue for 12 months/ TTP**

BDR

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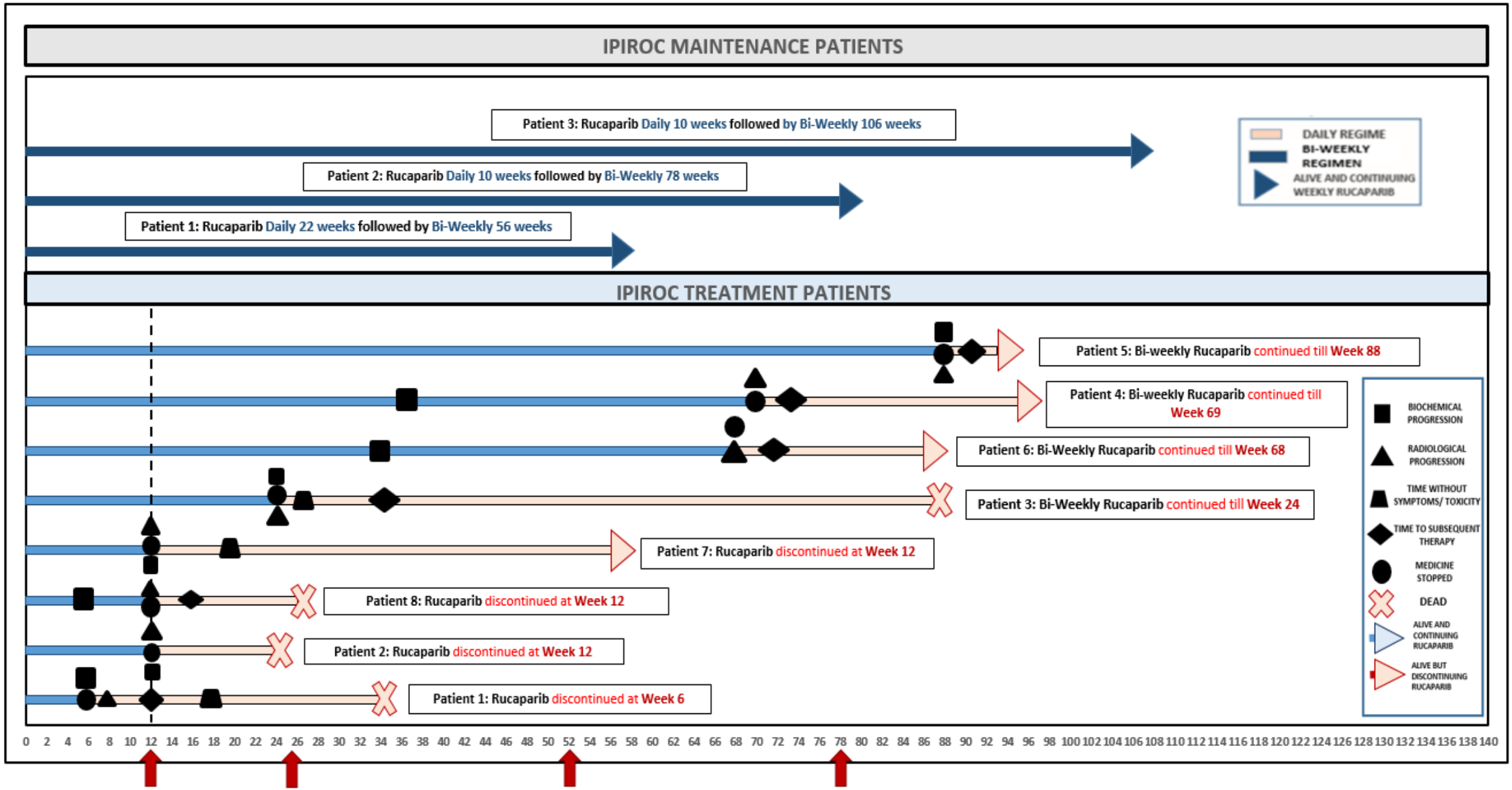
Department of Biotechnology
Ministry of Science & Technology
Government of India

KolGOTrg
Kolkata Gynaecological Oncology Trials and Translational Research Group

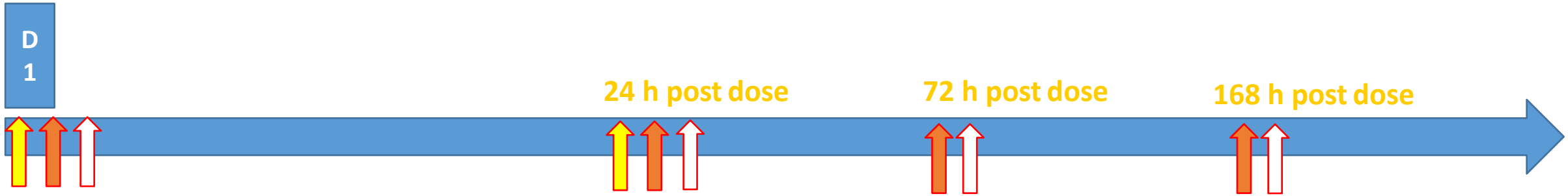
IPIROC #2 PROGRESSION CHART (Updated Up to Jan 2024)



IPIROC # 2: Translational studies in a subgroup (optional for many sites)

Translational study: Week 1: single dose PARPi ⟶ measure duration of PARP inhibition in PBMC/ascites (PD/PK) Pharmacogenomics/toxicity (MOREPARP)/functional HRD/ immune modulation

Target patient population: recurrent HGSOC, able to swallow a single dose of PARPi X, PS=0-3, able to comply with the protocol schedule visits for additional blood sampling (24 h, 72 h and 168 h time points have +/-4 hour window); 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

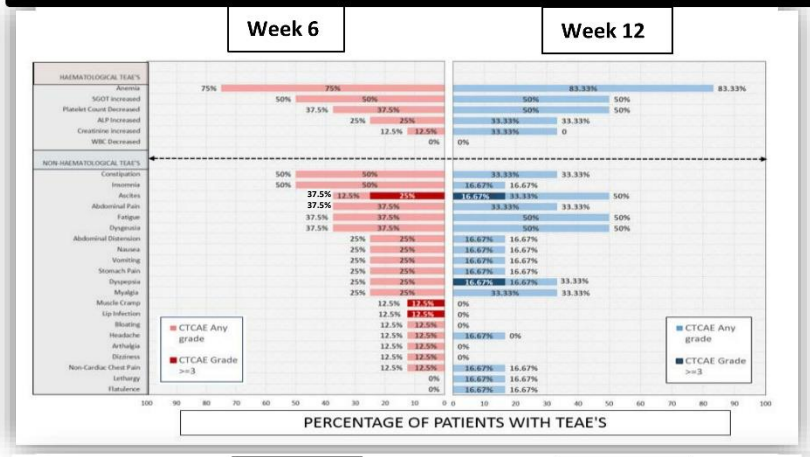
1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample PK
3. If patient undergoing ascitic drain fresh ascites sample (insert volume) for PD/PK drug levels prior to drain removal

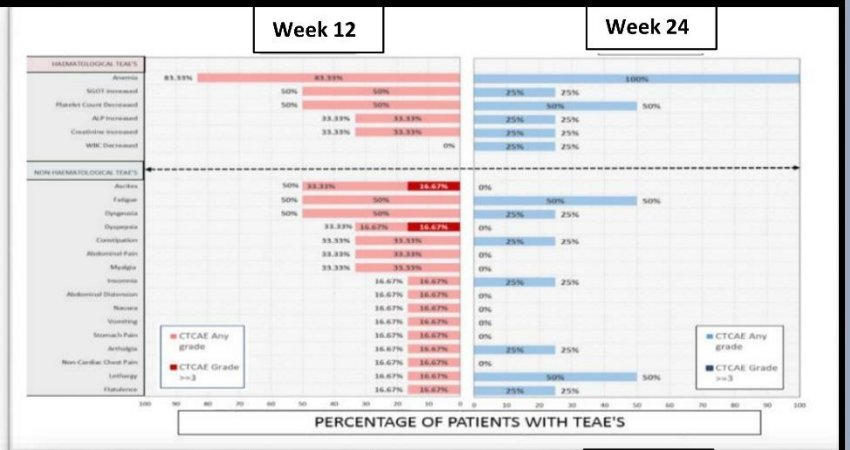
1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample for PK

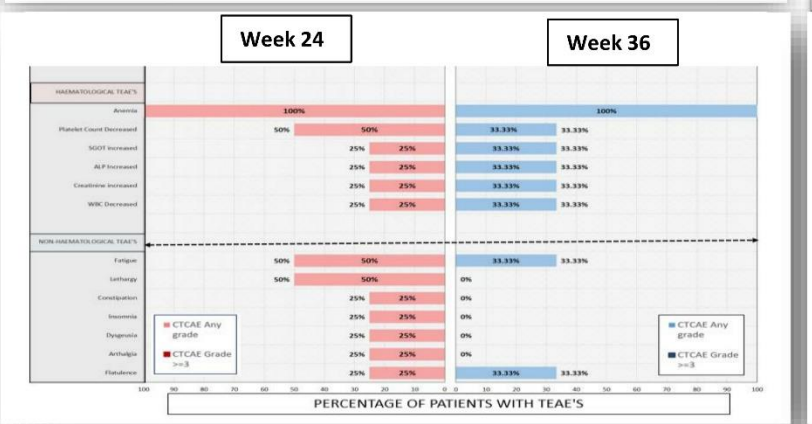
1. Whole blood 10 ml for PBL extraction for PARP activity
2. Blood sample for PK

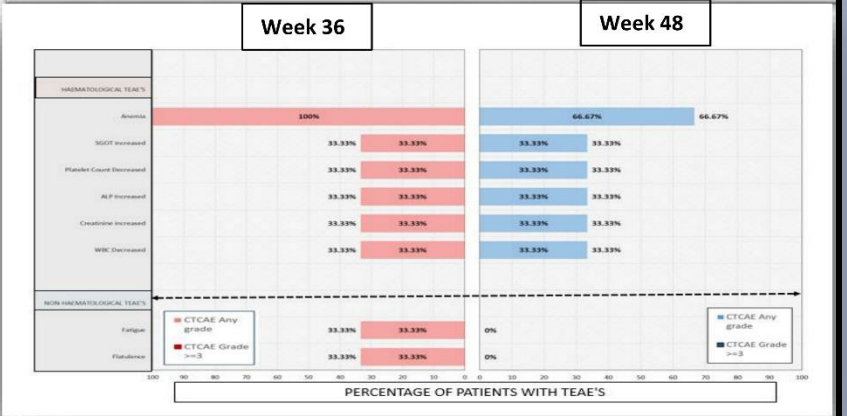
Q. Is there a way/is it necessary to normalise for the disease burden at recurrence?

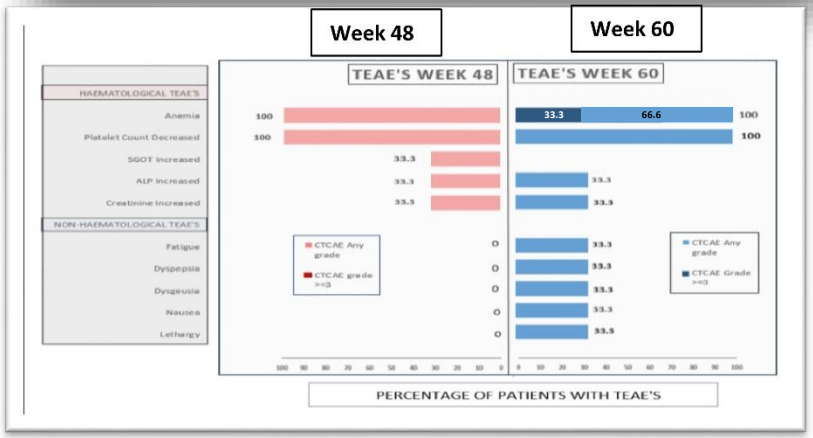
TEAE'S (UP TO WEEK 72): TREATMENT PATIENT

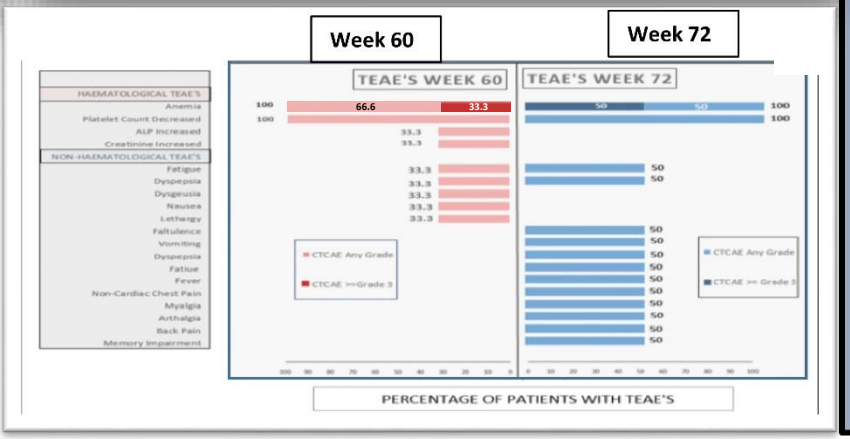




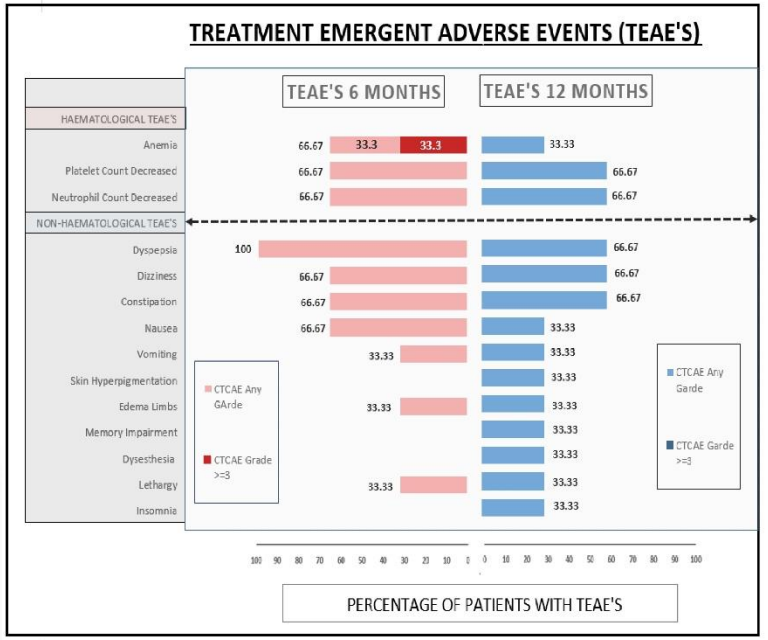


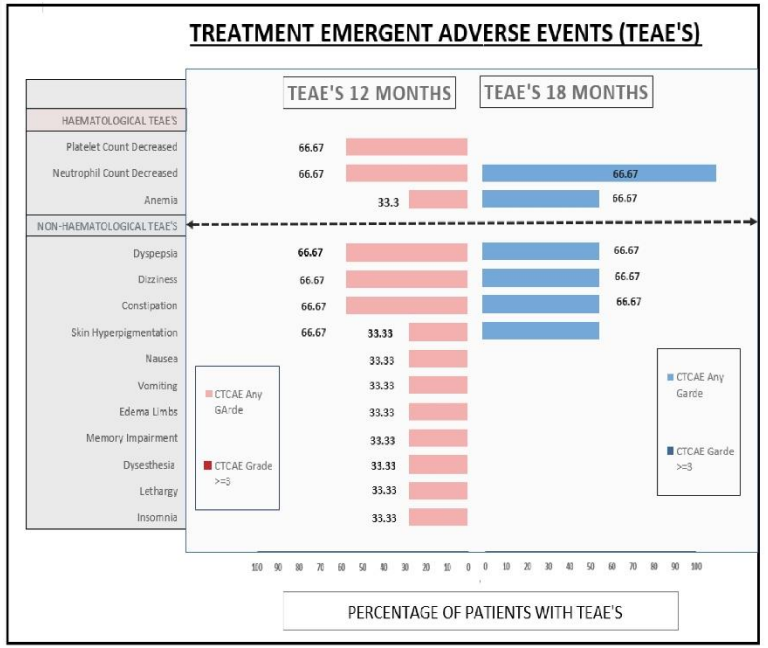






TEAE'S: MAINTENANCE PATIENTS





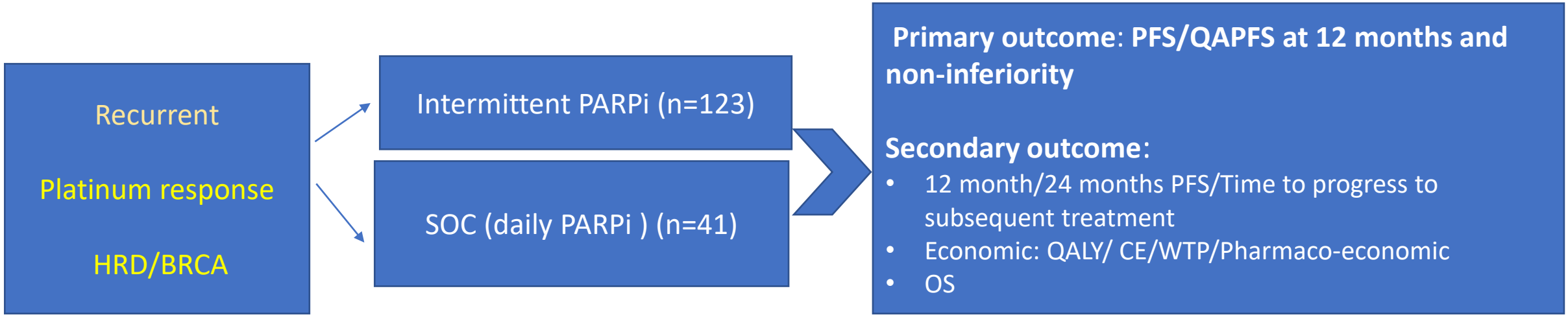
IPIROC # 3 (Intermittent PARP inhibitor regimen in ovarian cancer): Phase 2 RCT in HGSC

POC clinical trial for intermittent dosing PARPi with QOL-adjusted survival/toxicity/economic endpoints

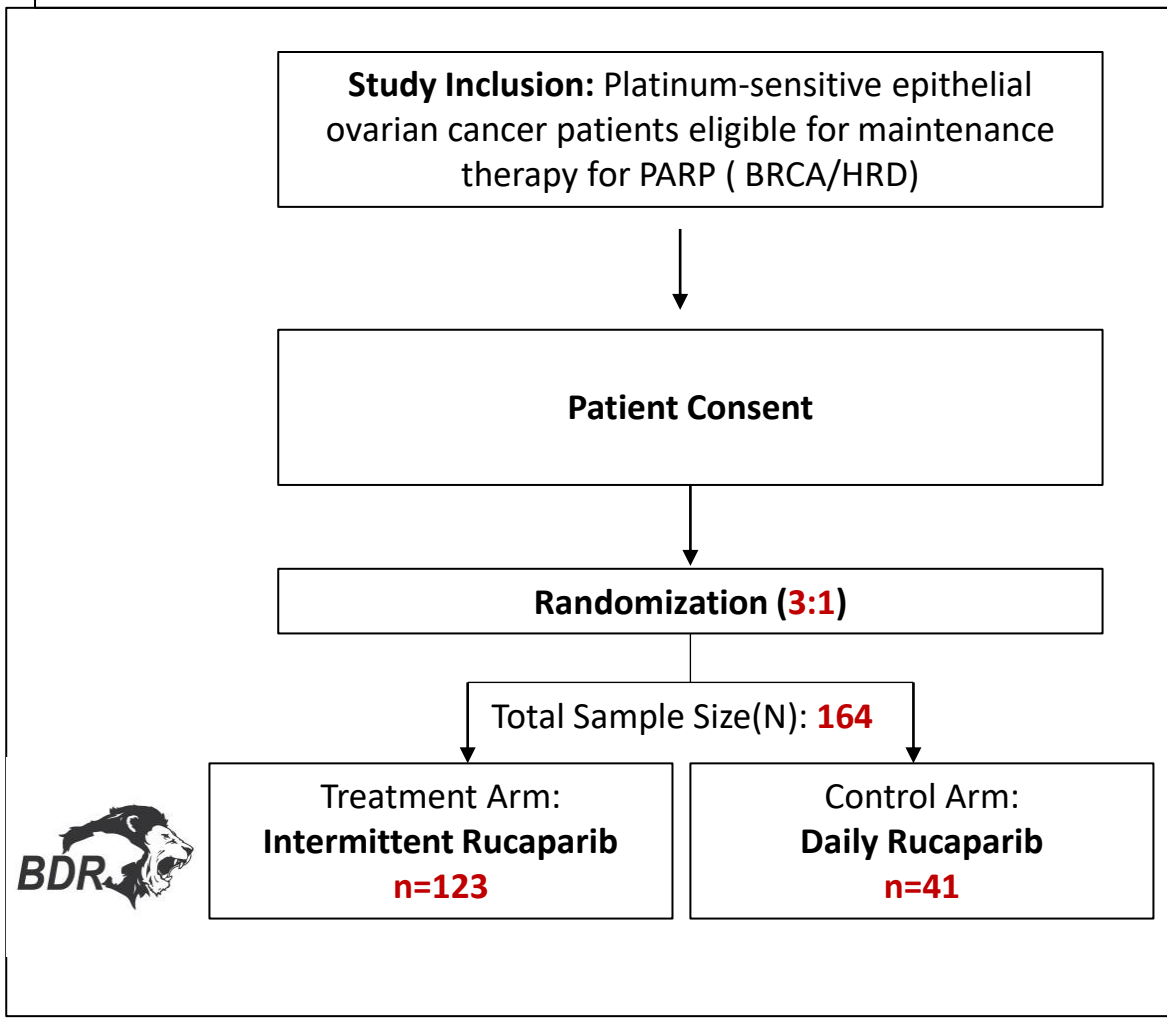
- Once we confirm that the modified schedule(s) is well tolerated and has acceptable response rate, we would begin a randomized phase 2/3 study using the intermittent schedule versus standard of care (SOC) [pragmatic approach] in frontline /recurrent settings as maintenance.

- 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: **QA PFS will be better in the experimental group.** A direct comparison of response rates or PFS using a non-inferiority (or an acceptable degree of inferiority) design would require larger number of patients (& resources)



Study Design # 1 (funded by ICMR)
Phase II Randomized Controlled Group Sequential Trial with an Adaptive design



Reference Publications: Patient-Centered Outcomes in ARIEL3, a Phase III, Randomized, Placebo-Controlled Trial of Rucaparib Maintenance Treatment in Patients with Recurrent Ovarian Carcinoma DOI: https://doi.org/10.1200/JCO.19.03107 ,
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial, doi: https://doi.org/10.1016/S0140-6736(17)32440-6

Study Design: QA-PFS for Intermittent Rucaparib (Treatment) is **non-inferior** to QA-PFS for Daily (Standard of Care) (Control)
Non-inferiority **margin** for HR (experiment/ control) = **1.5***
Hypothesis: H_0: **HR ≤ 1.5** **vs** H_1: **HR > 1.5**
Significance level = **0.10** Power = **80%**

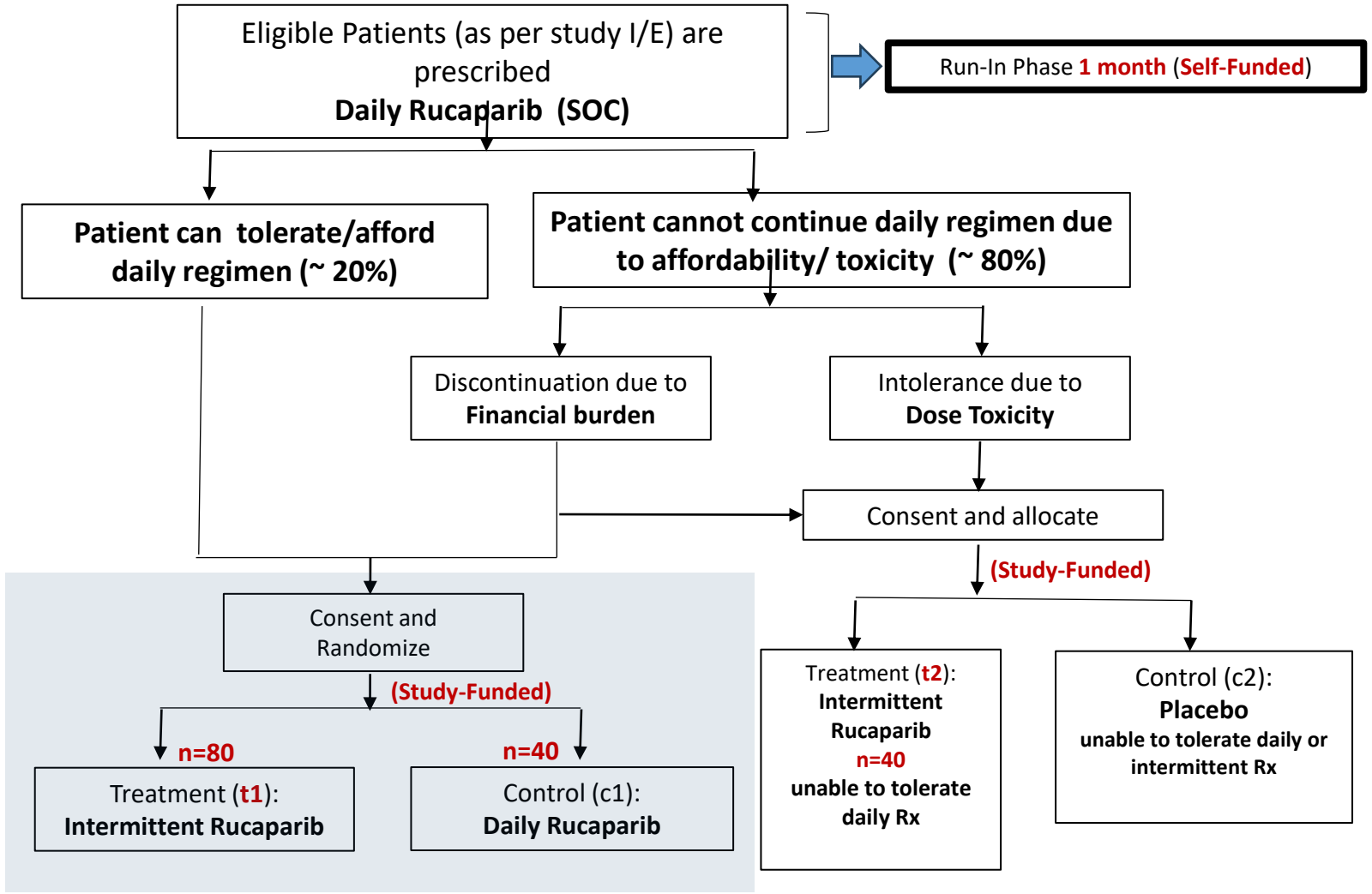
Randomization Allocation: **3:1** (Treatment vs Control)
Duration of Treatment: **12 months**
Follow-up Period: **2 years**

Sample Size: 164 (123 treatment vs 41 control) : Group Sequential Randomisation

Interim 1: **33** (25 treatment vs 8 control)
Interim 2: **66** (50 treatment vs 16 control)
Interim 3: **99** (74 treatment vs 25 control)
Interim 4: **132** (99 treatment vs 33 control)
Interim 5 [Final Analysis]: **164** (123 treatment vs 41 control)

*The **HR margin for non-inferiority** is taken as **1.5** for the above-mentioned model. **HR margin of 1.3** would have been **more appropriate**. But such a margin would have yielded a **total sample size** of **384** [**288** (Intermittent dose) vs **96** (Daily Dose)], which is more than twice our current sample size and will not be funded in he current grant scheme.

Modified Study design # 2 brainstormed for combatting the given problems:-



Questions related to this design:-

1) As the percentage of Dose-Intolerant patients in the run-in phase may be **high** (as per physician's/ expert's opinion), **including such patients in the originally proposed RCT would introduce biases when interpretating study results** and will also result in **requiring large sample sizes**

Moreover, these patients would not be eligible for original RCT GS Design (Intermittent vs Daily) as they are intolerable to Daily dosing.

The run-in phase will help identify patients who cannot tolerate daily does or experience financial burdens preventing them to continue participating in the study

Acceptable non-inferior (NI) PFS rate by 12 mths for intermittent group. NI measured as the uncertainty (lower 95% CI) being > 12mth PFS estimate in the control group, c1-10% . The historical median is 16.6mths => 12mth PFS ~60%. The total sample size i.e., t1, t2 and c1 is of 160

c2 will provide estimates from an observational cohort of PFS rates in patients who cannot tolerate Rucaparib (daily and intermittent) as well as patients who cannot afford intermittent (and daily) Rucaparib therapy

Design issues for current proposal:-

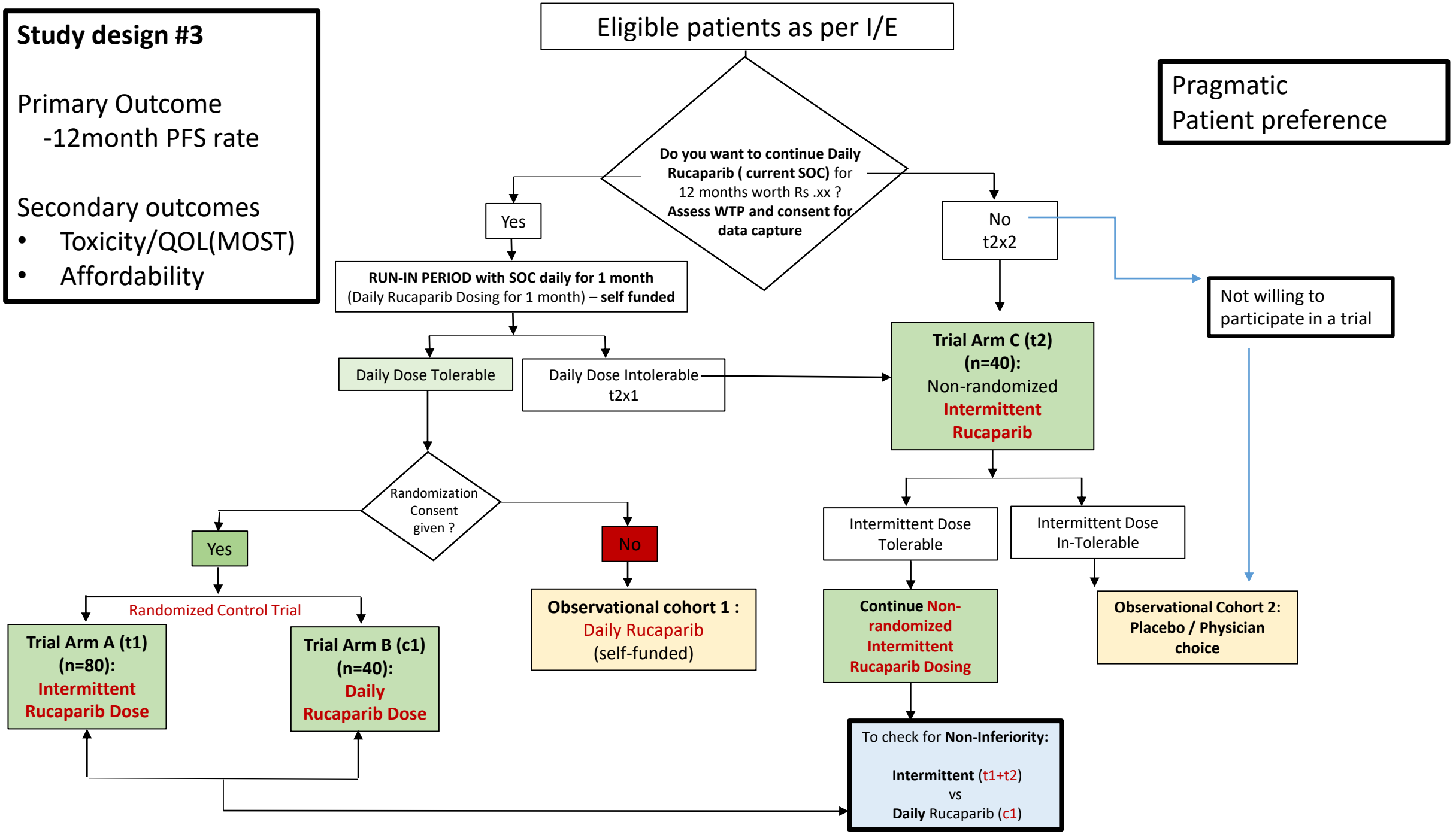
1) Randomized non-comparative phase II study with first cycle (xx weeks) being a run-in period which will identify patients who would not tolerate a daily dose of Rucaparib for a sustained period and/or would not be able to afford the cost of Rucaparib (daily/intermittent) as a potentially standard of care.
2) The patients identified in (1) will receive either placebo (***c2***) or commence on intermittent Rucaparib (***t2***) as appropriate (i.e., if the financial burden is not too onerous)
3) Patients allocated to ***t2*** but cannot tolerate the intermediate regimen will switch to ***c2***
4) Patients who can tolerate Rucaparib toxicity and do not experience an undue financial burden will be randomized (2:1) to receive intermittent Rucaparib ***t1*** or daily dose, ***c1*** (standard regimen)
5) The sample size for the randomized component is based on the selection design of Simon, Wittes, and Ellenberg.
6) In this design, we assume that a 12 mth PFS rate of 50% in the intermittent dosing group is considered interior to the daily dose having a 12mth PFS of ~60%. A sample size of 80 patients in the intermittent group will have > 89% probability that the 12mth PFS is > 50% if the regimen is truly non-inferior to the daily dose.
7) For 12mth PFS rates in the daily dose or < 60% or > 60%, a sample size of 80 will have > 90% probability to declare NI in the intermediate group based on a 10% margin.
8) While no formal comparisons of the study estimates of the 12 mth PFS rates are proposed (***t1*** vs ***c1***), as ***c1*** is a contemporary (randomized) control group, differences in estimates between ***t1*** and ***c1*** *will help inform design of future* (and potentially larger) studies to investigate the value of an intermittent regimen, especially in a NI setting.
9) Exploratory analyses between groups ***t1*** and ***t2; t1***+***t2*** and ***c1; t2*** and ***c1;*** as well as the outcomes in ***c2*** will provide insight as to PFS discrepancies due to treatment (a) affordability and (b) tolerability
10) The value of a run-in phase to identify tolerability/affordability will also be evaluated.

Study design #3

Primary Outcome
-12month PFS rate

Secondary outcomes
- Toxicity/QOL(MOST)
- Affordability

Pragmatic
Patient preference



Study participation options (non-interventional)

- Systematic review on EDI in PARPi trials
- Survey: Physician and patient on current practice of SOC
- Survey: Willingness to pay for cost-benefit analysis
- Registry: PARPi use in cancer

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Pragmatic Trial participation platforms for maintenance PARPi (interventional)

- Arm 1: Accepts to continue SOC (daily dosing) but does not consent for randomisation- Observational cohort 1
- Arm 2: Accepts to continue SOC and consents to be randomised in trial– Daily arm
- Arm 3: Accepts to continue SOC and consents to be randomised in trial– Intermittent arm
- Arm 4: Patient does not accept/ cannot tolerate SOC daily, but is willing to accept a trial for new SOC
  - Single arm non-randomised Intermittent arm
- Arm 5: Does not accept/tolerate SOC daily and is not willing to participate in any PARPi trial
  - Single arm physician's choice/ no maintenance- Observational cohort 2