HIPEC- HR [HIPEC in Homologous Recombination stratified ovarian cancer]

Asima Mukhopadhyay
Consultant Gynaecological Oncologist, CNCI Kolkata & NGOC, Gateshead UK

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

Study Design: Translational proof of concept (Targeted HIPEC) leading to Phase 2 RCT
Peer Review: Wellcome Trust DBT-IA Clinician Scientist award (fellowship)

GCIG Groups: KolGo Trg (Kolkata Gynecology Oncology Trials and Translational research group, India)
(KolGo-PROVAR-001).
(GCIG mentors: McNeish/Bookman/Oza) - (Discussed with UK and Canadian group members).

Sponsor(s): KolGo Trg/ Chittaranjan National Cancer Institute (CNCI) Kolkata
Presenter name and email: Email: asima7@yahoo.co.in

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

Role of HIPEC in an era of targeted therapy

- **In LMICs- majority of women/governments will not be able to afford targeted therapy (Bev/PARP). Financial drain (catastrophe) often limits majority of chemotherapy based treatment options at recurrence – OS is poor**

- **Improving surgical quality/expertise to perform primary surgery and addition of IP/HIPEC is perhaps the most cost effective way of improving PFS (at least by 3-4 months) and more importantly time to subsequent therapy**

- **HIPEC can add to post-operative morbidity/cost –especially in regions with gut microbiome showing high incidence of Gram negative MDRO.**

- **Additional cost of HIPEC is approximately (1500 USD). If a targeted approach for HIPEC is identified- even better!**

- **Even in high resource settings- can it be a cost effective alternative in a select subgroup of patients without compromising the PFS and thereby reserving the PARP for recurrence (less resistance?)**

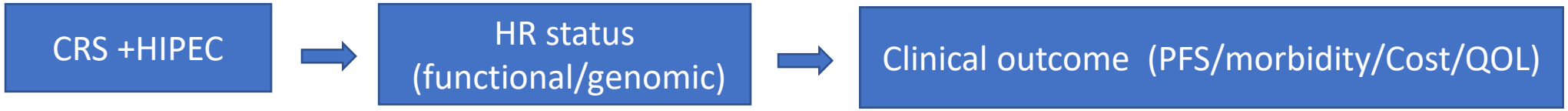
- **Can HR status aid in a better patient selection for intra peritoneal chemotherapy options including HIPEC; Which HRD assay?**

Summary of proposed study schema: 2 stages

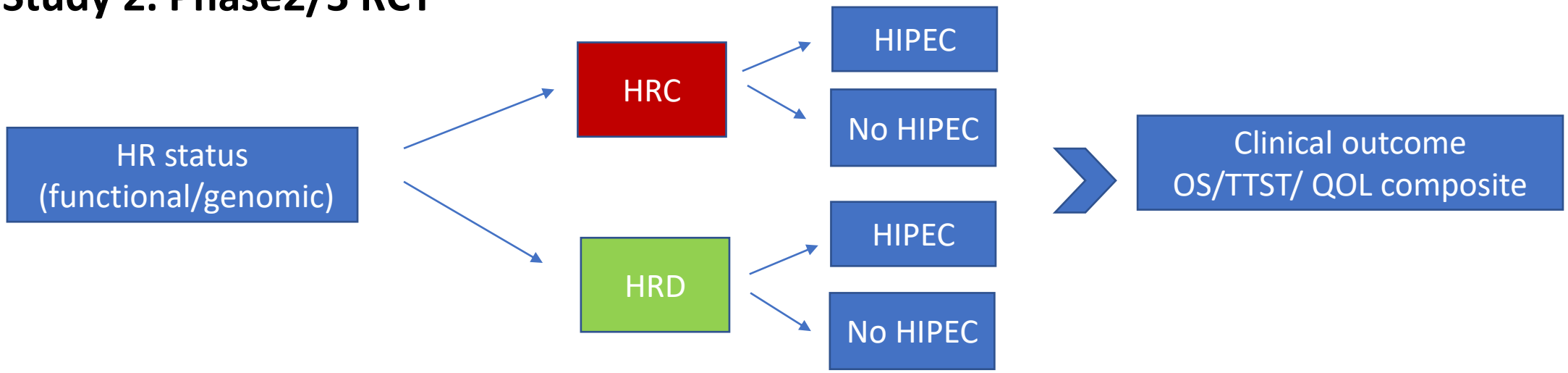
- **Study 1: Non-randomised single arm study (*will also allow time to build up on experience before going for a RCT)***

Clinical outcome: difference in efficacy/treatment outcome after CRS+ HIPEC in the frontline setting between HRC and HRD

Translational outcome: What does heat do on DDR and TME (Immune/ECM)- *Wellcome Trust IA CS*

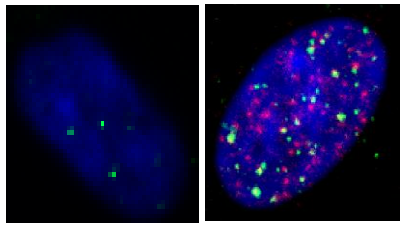


- **Study 2. Phase2/3 RCT**



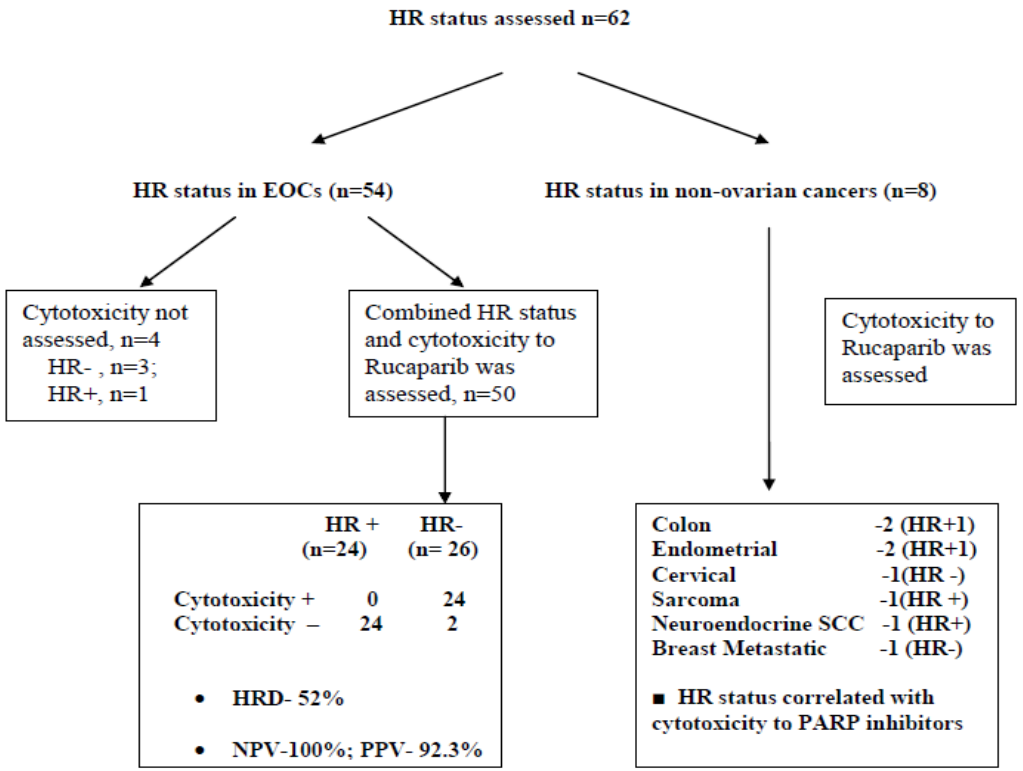
Origin of proposal: Previous and ongoing work:

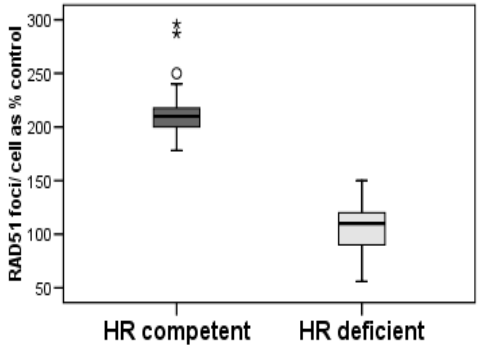
(Mukhopadhyay et al . Clin Cancer Research 2010; & Cancer Research 2012)



Rad 51 foci in PCO 61

RAD51 Immunofluorescence as a **functional assay** for HR (2010)





50% EOC are HRD

Development of other HRD assays

Clinico-pathological correlation

	HRC (24)	HRD (26)	
Complete /optimal cytoreduction	62.5%	80.8%	
CA 125 at presentation (median)	427	2079.50	0.007*
Serous Histology	62.5%	92.3%	0.035*
Platimun Sensitive	16.7%	53.8%	
Sensitivity to PARPi (AG014699)	0/24	24/26 (92.8%)	<0.001 **
OS 12 months(death)	41%	15%	
Median PFS In months	8	11	

Irrespective of Site of origin (ovarian/non ovarian): Functional HRD status predicted ex-vivo chemosensitivity to PARPi (AG014699). NPV 100%; PPV 92.3%

AACR DNA repair 2016
Abstract # A05

Improving outcome in Homologous recombination competent epithelial ovarian cancer: Hyperthermia and Surgeon's perspective

Asima Mukhopadhyay[1, 2], Ganiy Abdulrahman [2], Eliza Davison[2], Elizabeth Matheson[2], Yvette Drew[2], Helen Bryant[3], Nicola Curtin [1]
[1,2] Tata Medical Center and Tata Translational Research Center, Kolkata, India
[2] Northern Institute for Cancer Research, Newcastle University, UK [3] Sheffield Institute for Nucleic Acids, Sheffield, UK

Introduction

- We developed a functional assay and showed that 50% epithelial ovarian cancers (EOCs) are homologous recombination (HR) deficient (HRD) and are sensitive to PARP inhibition[1]. HRD patients showed also improved clinical platinum sensitivity (53.8% vs 16.7%), survival (12 month OS- 41.7% vs 11.5%) and optimal cytoreduction (80% vs. 62%) rates compared to HR competent (HRC) tumours which represent an **unmet clinical need requiring novel therapeutic strategies for both surgery and chemotherapy.**
- HIPEC (hyperthermic intraperitoneal chemotherapy) has been shown to improve survival in ovarian cancer. Preclinical data indicate that hyperthermia compromises HR, possibly by protein unfolding. Chaperone proteins such as HSP90 are required for re-folding and inhibitors (HSP90i) are being investigated to render these cells HR deficient, and therefore sensitising them to PARPi. [2] There is controversy however over the optimum temperature required to prevent damage to normal tissues and also whether both platinum/PARPi sensitive and resistant cancers will benefit from HIPEC.
- **We hypothesize**
  1. **Hyperthermia compromises HRR function**
  2. **HRC tumours will benefit from targeted HIPEC following primary surgery and HSP90 inhibitors**

Methods

- HRC cell lines (VC8-B2, UWB1.289+BRCA1, A2780) and HRD cell lines (VC8, UWB1.289) were used.
- RAD51 foci, a marker of HRR, and γH2AX foci, a marker of DNA damage, were measured after treatment with heat at 39°C and

Results

Figure 1. HSP90 inhibition and incubation at 39ºC both resulted in a modest sensitisation to rucaparib

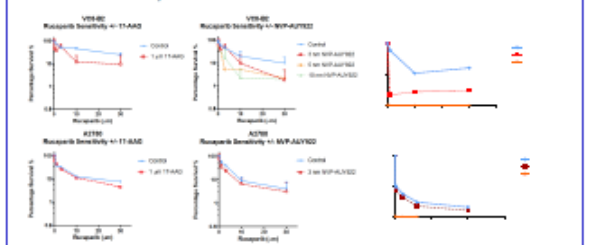


Fig1. Results of clonogenic survival assays and concentration-response to rucaparib in VC8, VC8-B2 cells and A2780 cells, either with HSP90 inhibition or in hyperthermic conditions. 1 hr incubation at 42ºC caused total cell death but at 39ºC, viability was 25% and sensitised V-C8 B2 (HRC) cells, but not V-C8 cells to rucaparib.

Figure 2. Heat at 42ºC sensitized UW+B1 (BRCA 1 competent) cells to olaparib (PARP inhibitor) but UW cells (BRCA1 deficient) all died. WB showed that 42ºC degrades BRCA2 but not BRCA1. *(Helen Bryant, Sheffield, UK)*

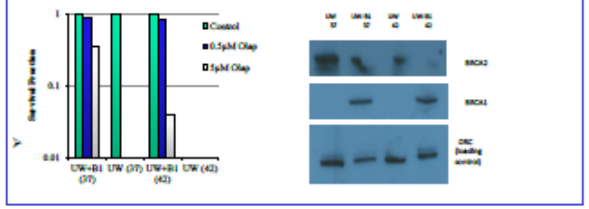


Figure 3. HSP90 inhibitors reduce RAD51 foci formation in a concentration-dependent manner and levels of RAD51 in WB

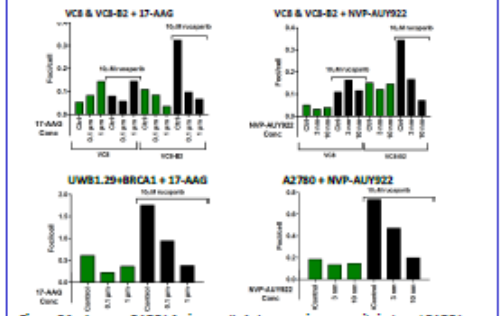


Figure 3A. Average RAD51 foci per cell. A decrease in rucaparib-induced RAD51 foci can be seen across all cell lines with increasing concentrations of HSP90i

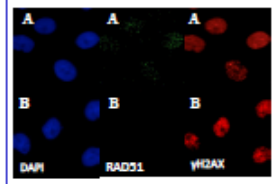


Figure 3B. Immunofluorescence microscopy of UWB 1.29+BCRCA1 cells, showing a decrease in RAD51 with 1 μm 17-AAG (B) when compared with control (A). In all cell lines, rucaparib-induced RAD51 foci decreased on average by 79% with 1 μm 17-AAG and 76% with 10 nm NVP-AUY922.

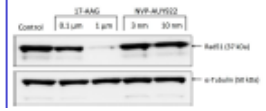


Figure 3C. Western Blot in A2780 cells, with varying concentrations of 17-AAG and NVP-AUY922. RAD51 foci decreased with increasing concentrations of 17-AAG, with almost no expression visible at 1 μm.

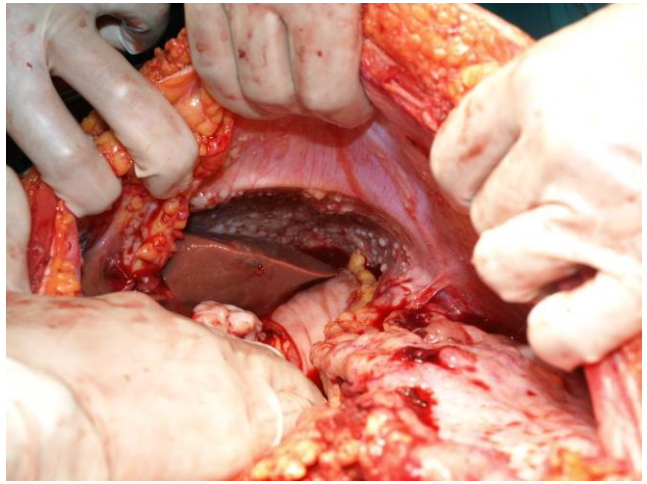
Improving outcome in Homologous competent epithelial ovarian cancers: Hyperthermia and surgeon's perspective: AACR DNA repair 2016

Pilot pre-clinical data: Heat at 42 ºC sensitizes BRCA proficient HRC cell lines to PARPi, BRCA2 is down regulated

Ongoing work: (UKIERI grant/ Wellcome Trust IA CS) – Ex vivo

- **Heat and PARP activity In HRC vs HRD**
- **Heat and PARP inhibitor sequence**
- **Heat at 39-40 ºC vs 42 ºC**
- **Duration of effect after heat**

Surgeon's Lab: Observing heterogeneity, tumour distribution and character/stiffness and interaction with micro-environment affecting outcome/ toxicity



Heat on TME in HRC vs HRD

- **? Immune escape mechanism/ECM matrix modulation is different between HRC and HRD**
- **? Is there differential response to heat affecting different micro-environments?**

Initial idea of the Concept of Targeted HIPEC in 2014 (AACR DNA repair,2016)

Epithelial ovarian cancer- tumour tissue study for biomarker

HRC

Primary surgery+ **HIPEC**

Adjuvant selective HR inhibitors based on expression of HR proteins/ pathways + platinum/ PARPi

Benefit- Survival, improved chemoresponse. Also quality of life and time by averting inappropriate use of NACT in poor chemo-responders

HRD

NACT or primary surgery, IP chemo role for PARP1 in either setting (HIPEC at 39 degree?)

In select cases with good chemoresponse to NACT, may consider limited surgery like BSO only or delayed surgery at recurrence ±HIPEC; assess HR status again and targeted chemotherapy

Benefit- Quality of life, limited extent of surgery/ delayed surgery without compromising survival as expected to be good chemo-responders

Hypothesis: HIPEC may be targeted/selectively used in the HRC subgroup due to compromise on DDR/immune escape (turn cold tumour to hot)/ ECM modulation.
(*Effect size/benefit may be larger in this subgroup rather than subjecting everyone (HRD) where standard chemotherapy/other alternatives work or may be better)*

Study 1: Non-randomised single arm study (*will also allow time to build up on experience before going for a RCT)*

- **To study if there is a difference in efficacy/treatment outcome after CRS+ HIPEC in the frontline setting between HRC and HRD EOC** *or*
- To assess whether HR status is a prognostic biomarker for treatment outcome following primary/frontline CRS and HIPEC (Intervention) [comparator CRS and no HIPEC]

Inclusion Criteria

- **candidate for primary CRS , ECOG< 2**
- **histological or cytological proven HGSC, FIGO stage III**
- **Optimal cytoreduction (CC/CC1)**
- **Fit for HIPEC at the end of CRS**

HIPEC-cisplatin 100 mg/m2/90 min, **42 º C**

HR status will be known after Intervention

HRC- 50%

HRD- 50%

SOC adjuvant chemotherapy (6 cycles C+T)
? Separate subgroup for Bev/PARP maintenance

Surgical and Lab QA: ESGO criteria/equivalent; Experience in HIPEC at least 10 procedures

Assessment of HR status (chemo-naïve ideal): T1

- Functional: gammaH2AX/Rad51/Geminin assay or RECAP assay
- Genomic: My Choice (*others ? Shallow sequencing/mutational signature-optional/translational*)

Outcome measure:

1. Clinical outcome

a)**Time to progress** b)Time to subsequent therapy c)Complications/toxicity
c) Cost of treatment d) Quality of life /composite endpoints

2. **Translational outcomes:** T2 Pre & T3 post heat tissue samples to study effect of heat on (structure and/or function) (smaller subset of patients)

a) DDR/HR status – functional status
b) ECM modulation- stiffness (desmoplasia score/matrisome index)
c) Immune cell infiltrates and function (spatial and functional assay)

Statistical Considerations and questions

- **Simplest/pragmatic way-** each center starts HIPEC in PDS (/IDS) as a surgical feasibility study following the surgical QA/benchmarking and then audit their respective treatment outcomes.

  HR status is assessed (translational component –research) and then data is pooled for analysis.

  (*In this way- each potential center will have opportunity to perform 15-20 cases prior to preparing for participation in RCT*).

- Do we need a historical /matched control (Surgical QA maintained) with no HIPEC but known HRD status to estimate the benefit of HIPEC in HRC (and HRD)

- PFS in HRC subgroup is variable - 8 months in CCR study in 2012(70% PDS) vs 5.4 months in PRIMA study in 2019 (66% IDS). Should we include IDS (if COVID continues!).

- Separately analyze patients who would be on Bev/PARP and add on numbers needed for statistical analysis (This will have impact on site /group selection)

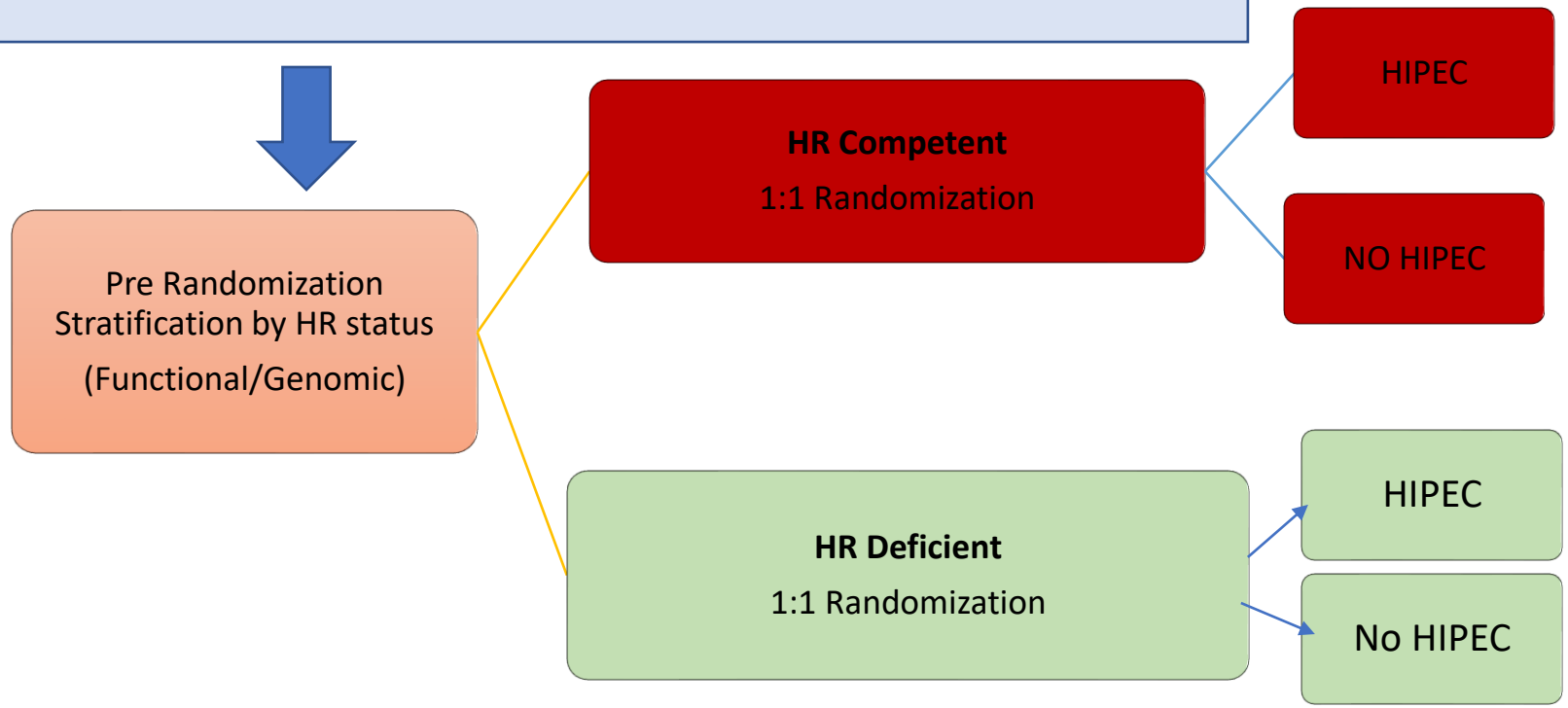
- Choice of HRD assay (Genomic and functional both or optional)

Planned accrual: Start 2021 (mid-end)

(Centers in India, n=4; other groups/centers - ?OCRN)

Study 2 (after study 1 is complete): Randomised Phase 2/3 study (possible design)

- CRS+ HIPEC in frontline setting (PDS/IDS)
- FIGO Stage 3 /4
- Optimal CTR (< 2.5mm RD and <1 cm RD)
- Adjuvant SOC includes C+T only and also maintenance Bev/PARP in centres where it is the SOC



Outcome measure

OS
TTST
Economic

Acknowledgement

Newcastle University / Centre for Cancer

Nicola Curtin
Yvette Drew
Luke Vale

NGOC Northern Gynaecological Oncology Centre

William Helm
Ann Fisher
Christine Ang
Stuart Rundle

CNCI

SAROJ GUPTA CANCER CENTRE & RESEARCH INSTITUTE

TATA MEDICAL CENTER

CSIR-Indian Institute of Chemical Biology

IISER KOLKATA

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UK-India Education and Research Initiative

wellcome trust DBT INDIA ALLIANCE

CANCER RESEARCH UK

Department of Biotechnology
Ministry of Science & Technology
Government of India

KolGOTrg
Kolkata Gynaecological Oncology Trials and Translational Research Group

Rahul Roy Chowdhury
Biman Chakraborty
Ranajit Mandal
Santanu Tripathi
Sanjoy Paul
Rakesh Roy
G S Bhattacharya
Chanchal Goswami
KK Mukherjee
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Dona Chakrabarty
Aparajita Bhattacharya
Twinkle Sinha
Mou Das
Ajit Mukhopadhyay

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An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Michael Bookman
Amit Oza
Iain McNeish
Mary McCormack
UCL CTU
Ted Trimble

Collaborators

Neerja Bhatla
Somasekhar SP
Ranjit Manchanda
Frances Balkwill
Subhra Biswas
Dipanjan Chowdhury
Roland Kanaar
Dik C van Gent
Helen Bryant

strand
JIV DAYA FOUNDATION Dallas Texas
MEDGENOME