Hyperthermia and immune modulation in homologous recombination stratified epithelial ovarian cancer: Rationale for developing a clinical trial of HIPEC vs IP Chemotherapy with translational end points and a targeted therapy approach

Asima Mukhopadhyay ^{1,2,} 1 Department of Gynaecological Oncology, Tata Medical Center, Kolkata, 2. Northern Institute of Cancer Research, Newcastle University, UK Wellcome Trust IA Clinician Scientist Fellow

Origin of proposal: Previous and ongoing work: Bench Clinic Bench

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

Functional assay of Homologous recombination (HR) deficiency from primary tissue material



Research questions:

- Is heat beneficial over and above IP chemo
- ? Immune escape mechanism is different between HRC and HRD- Is there differential response to heat affecting different micro-environment?
- **Personalised therapy/surgery** using different approaches for HRC and HRD



HRC (24) HRD (26)

Complete */***optimal cytoreduction**

62.5% 80.8%

CA 125 at presentation (median)

62.5%

427 **Serous Histology**

0.007* 2079.50

92.3% 0.035*

53.8%

Platimun Sensitive 16.7%

Sensitivity to PARPi

0/24 24/26 (92.8%) <0.001 **

OS 12 months (death)

15%

Experimental Plan:

1.Clinical study-

To assess feasibility and toxicity of HIPEC versus standard IP/systemic chemo after surgery 2. Translational-

To assess the effect of hyperthermia/HIPEC on DNA damage response and immune escape mechanism in HRC versus HRD EOC

> **HIPEC -HRC HIPEC -HRD** Survival, toxicity QOL, **IP-HRC IP -HRD** Cost

What next?

1. What to do with the other 50% that are HR competent EOC?

-Can functional HRD phenotype be induced (HR inhibition) - Imatinib/ Pi3K /HDAC/ HSP90 inhibitor - Hyperthermia

2. Does HR status alter its microenvironment too to benefit survival?

- HR competent tumours will have increased mesenchymal phenotype/ inflammation-fibrosis/ / immune escape which can affect surgical resectability



WP 1: Clinical trial Year 1-2: Phase 2 non randomised in advanced EOC HIPEC (n=25) vs no HIPEC (IP/IV chemo, n=25) following CRS Year 3: Analysis of complications, toxicity, efficacy, immune scoring strategies from FFPE cost, QOL, PFS Year4-5: Continue phase 2 design/ pilot phase 3 RCT in subsets pre and post HIPEC comparing HIPEC (n=25)and IP chemotherapy following CRS (n=25 heat/immune modulators Tissue collection: Tumour tissue/ascites and blood Pre and post surgery (before starting Chemo) Pre and post normothermic IP/IV Pre and post HIPEC Development Learning **Clinical questions** Clinical academic team/trial Does heat really add to unit and training capable of normothermic IP • Develop pre-clinical conducting: chemotherapy (has not models for surgical-clinical been compared head to application -i.e. 3-D Basket/umbrella trials with head) primary culture models for surgical/clinical application mechanistic studies on - Trials with translational • If yes, what is the toxicity

WP2: Translational studies

Year 1-2: Stratify HR status by functional HR assay in 2D primary cultures and/or NGS DNA based HRD panel assay HRC vs HRD (estimate 50: 50) Study effect on DAMP and HR compromise +/- heat

Year 3: Develop 3D culture models (BCI, London) and

Year 4-5: Immune scoring on HRC and HRD EOC (n=100) and Immune phenotyping and functional T cell studies in specific subsets (collaboration-Medgenome) Mechanistic studies in 3D models (HRC/HRD) pre and post

Animal studies at IISER, Kolkata (parallel ongoing project)contribute a subset of animal tissues for effect on DAMP and DNA damage response following post IP chemo vs. HIPEC

Rationale for targeted HIPEC (Hyperthermic Intraperitoneal Chemotherapy)

- Morbidity/ cost Recent RCT: improves survival • Heat at 39-40 degree- immune/ inflammation axis • Heat at 42 degree- compromise DNA repair
- Pilot pre-clinical data: Heat sensitizes BRCA proficient HRC cell lines to PARPi, BRCA2 is down **regulated-** Mukhopadhyay et al, AACR DNA repair, 2016

Corresponding author:

asima.mukhopadhyay@tmckolkata.com Nicola Curtin, Newcastle University, UK William Helm, Royal Cornwall Hospital, Truro, UK Ranjit Manchanda, Barts Health NHS UK, London

