Some rules for the videoconference

- Please keep yourself muted
- Please, do not over-run your time
- Please, do not speak at the same time
- After each new concept questions will be addressed
- For all other presentations questions will be taken at the end of each session
- If you have a question or a comment rise your hand in the zoom system or send a text using the chat
- After the presentation of new ideas, interested groups should send an email to the presenter
PHASE II COMMITTEE
TUESDAY, MAY 26, 2020, 8:00 EDT; 14:00 CET
Chair: Mansoor Mirza  Co-Chair: Alexandra Leary
Harmonization Liaisons: XXX(Ops); Paul (Stats)

AGENDA

Welcome & Introductions: Mirza
COI declarations:
Approval of Minutes/Report: November 2019 (posted on GCIG website)
Motion: ________________________________ Seconded: _________________________

New Concepts/Proposals (max 5 slides):
KGOG OPEB-01 Jung-Yun Lee
KolGOTrg IPIROC Asima Mukhopadhyay
KolGOTrg HIPEC-HR Asima Mukhopadhyay

Update of Trials in Development (max 3 slides):
MITO 25.1 Domenica Lorusso
CCTG DOMINO Stephen Welch

Summary of ongoing trials without substantial new information (1 slide):
KGOG 3046 TRU-D Jung-Yun Lee
KGOG 3045 Jung-Yun Lee
ENGOT-OV30 / NSGO-Umbrella Mirza

Closed for enrollement / Published Trials (1 slide):
ENGOT-OV24 / NSGO-AVANOVA Mirza
ENGOT-EN2 / NSGO Mirza
ENGOT-EN1 / NSGO-FANDANGO Mirza
ENGOT-EN3 / NSGO-PALEO Mirza
A single-arm phase II study of Olaparib maintenance with Bevacizumab & Pembrolizumab in BRCA non-mutated patients with platinum-sensitive recurrent ovarian cancer

Trial setting: ovarian cancer/platinum-sensitive
Study Design: a phase II study
Participating Groups: KGOG, GCGS
Sponsor: Yonsei University College of Medicine
Status: Not yet recruiting
Grant support: Not determined
Drug supply: MSD

NCT04361370
OPEB-01
Single arm phase II, Total n=44
Primary endpoint: 6 months PFS rate

Recurrent BRCA wild-type OC
Nonmucinous OC
No Germline and tumor BRCA mutation
≥6 mon after 1st line CT
ECOG 0 or 1

Platinum-based chemo ± Bevacizumab

Olaparib + Pembrolizumab + Bevacizumab

Simon’s two-stage optimal design
5% sig, 1-sided α; 80% power
H0 6m PFS rate = 50%; H1 6m PFS rate = 70%
Intermittent PARP Inhibitor in Recurrent Ovarian Cancer (IPIROC)
Asima Mukhopadhyay
Consultant Gynaecological Oncologist, CNCI Kolkata & NGOC, Gateshead UK

**Trial setting:** Recurrent ovarian cancer
**Trial status** – New Concept development stage

**Trial Model:** Academic (A)

**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

**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
**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.
Figure 1. The first in human clinical trial, a Phase 1 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/m² (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

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

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: 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/PK)- find out the optimal duration of inhibition/intervals

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

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 (24 h, 72 h and 168 h time points have +/-4 hour window); Single oral dose PARP inhibitor X given at time zero

Curtin, Drew, 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 (1\textsuperscript{st} or 2\textsuperscript{nd}) 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

Primary outcome: **QTWIST**
- Time to progress/ Time to toxicity

Secondary outcome:
- Response rate (RECIST and Ca125)
- PFS/Time to progress to subsequent treatment
- Economic: QALY/ CE/WTP/Pharmaco-economic

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

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

Rahul Roy Chowdhury
Biman Chakraborty
Ranajit Mandal
Santanu Tripathi
Sanjoy Paul
Rakesh Roy
G S Bhattacharya
Chanchal Goswami
KK Mukherjee
Jaydip Bhaumik
Tamohan Chowdhury
Chandan Mandal
Susanta Roy Chowdhury
Jayasri Das Sarma
Indrani Roy Chowdhury
Mitali Chatterjee
Vilas Nasare
Benubrata Das
Chitra Mandal
Sibsankar Roy
Shilpak Chatterjee
Jayanta Chakrabarty
Tapas Maji
Dipanwita Banerjee
Manisha Vernekar
Basumita Chakraborty
SS Mondal
Chinmoy Panda
Sharmila Sengupta
Shuvojit Moulik
Siddikuzzaman
Asama Mukherjee
Ratnaprabha Maji
Bijoy Kar
Vaishali Mulchandani
Supriya Mondal
Barnali Ghosh
Dona Chakraborty
Aparajita Bhattacharya
Twinkle Sinha
Mou Das
Ajit Mukhopadhyay

Collaborators
Neerja Bhatla
Lalit Kumar

Michael Bookman
Amit Oza
Iain McNeish
Mary McCormack
UCL CTU
Ted Trimble
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 status – New Concept development stage

Trial Model: Academic (A)

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?

Proposed study plan summary:

Study #1:
Non randomised single arm study
• Frontline CRS HIPEC– HR status
• Clinical and translational outcome

Study #2:
Randomised Phase 2/3 study
HR status – HRD or HRC (functional/genomic)
HRD- 1:1 randomisation- HIPEC vs no HIPEC
HRC- 1:1 randomisation – HIPEC vs no HIPEC
Origin of proposal: Previous and ongoing work:


Clinico-pathological correlation

<table>
<thead>
<tr>
<th></th>
<th>HRC (24)</th>
<th>HRD (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete /optimal cytoreduction</td>
<td>62.5%</td>
<td>80.8%</td>
</tr>
<tr>
<td>CA 125 at presentation (median)</td>
<td>427</td>
<td>2079.50</td>
</tr>
<tr>
<td>Serous Histology</td>
<td>62.5%</td>
<td>92.3%</td>
</tr>
<tr>
<td>Platinun Sensitive</td>
<td>16.7%</td>
<td>53.8%</td>
</tr>
<tr>
<td>Sensitivity to PARPi (AG014699)</td>
<td>0/24</td>
<td>24/26 (92.8%)</td>
</tr>
<tr>
<td>OS 12 months (death)</td>
<td>41%</td>
<td>15%</td>
</tr>
<tr>
<td>Median PFS In months</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

Irrespective of Site of origin (ovarian/non ovarian): Functional HRD status predicted ex-vivo chemosensitivity to PARPi (AG014699). NPV 100%; PPV 92.3%
**Initial idea of the Concept of Targeted HIPEC in 2014 (AACR DNA repair, 2016)**

*Improving outcome in Homologous competent epithelial ovarian cancers: Hyperthermia and surgeon’s perspective*

---

**Surgeon’s Lab:** Observing heterogeneity, tumour distribution and character/stiffness and interaction with TME in HRD vs HRC

- **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)

---

**Ongoing work:** (UKIERI/ Wellcome) – Ex vivo

- Heat and PARP activity in HRC vs HRD
- Heat and PARP inhibitor sequence
- Heat at 39-40 °C vs 42 °C
- Duration of effect after heat

---

**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/chemoresponse, QOL/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?)

---

**Heat at 42 °C sensitizes BRCA proficient HRC cell lines to PARPi, BRCA2 is down regulated**

---

Heat at 42 °C sensitizes BRCA proficient HRC cell lines to PARPi, BRCA2 is down regulated.
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;  \(?\)IDS- PFS varies
- histological or cytological proven HGSC, FIGO stage III
- Optimal cytoreduction (CC/CC1)
- Fit for HIPEC at the end of CRS

**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-optimal/translational)*

**Outcome measure:**

1. Clinical outcome
   - a) *Time to progress*  
   - b) Time to subsequent therapy  
   - c) Complications/toxicity  
   - d) 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)

**HIPEC-cisplatin 100 mg/m2/90 min, 42 °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  
? *Historical/matched control* with known HR status
**Study #2. Randomised Phase 2/3 study (possible design) (after study 1 is complete)**

- **Pre Randomization Stratification by HR status (Functional/Genomic)**
  - HR Competent
    - 1:1 Randomization
      - HIPEC
      - NO HIPEC
  - HR Deficient
    - 1:1 Randomization
      - HIPEC
      - No HIPEC

**Outcome measure**
- OS/ PFS
- TTST/QaPFS
- Economic

---

**Study #1. 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 as 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).

**Planned accrual study 1:** Start 2021 (mid-end)
(Centers in India, n=4; other groups/centers - ?OCRN)
Acknowledgement

Rahul Roy Chowdhury
Biman Chakraborty
Ranajit Mandal
Santanu Tripathi
Sanjoy Paul
Rakesh Roy
G S Bhattacharya
Chanchal Goswami
KK Mukherjee
Jaydip Bhaumik
Tamohan Chowdhury
Chandan Mandal
Susanta RoyChowdhury
Jayasri Das Sarma
Indrani RoyChowdhury
Mitali Chatterjee
Vilas Nasare
Benubrata Das
Chitra Mandal
Sibsankar Roy
Shilpak Chatterjee
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- ENGOT-EN3 / NSGO-PALEO Mirza
A randomized, molecular driven, phase II trial of Carboplatin-Paclitaxel-Bevacizumab vs Carboplatin-Paclitaxel-Bevacizumab-Rucaparib vs Carboplatin-Paclitaxel-Rucaparib, selected according to HRD status, in patients with advanced (stage III B-C-IV) ovarian, primary peritoneal and Fallopian tube cancer preceded by a phase I dose escalation study on Rucaparib-Bevacizumab combination

**Trial setting:** patients with advanced (stage IIIB-C-IV) ovarian, primary peritoneal and Fallopian tube cancer

**Study Design:** multicenter, phase I/II, open labeled, randomized, controlled study

**Sponsor(s):** Fondazione Policlinico A. Gemelli IRCCS of Rome

**Planned N° of patients:** 290

**Planned study start:** 01/07/2020
FIGO stage IIIB-C-IV high grade serous or endometrioid ovarian cancer, primary peritoneal and/or fallopian-tube cancer

**STRATIFICATION FACTORS:**

1) Residual tumor at primary surgery (RT=0 vs RT>0)
2) Neoadjuvant chemotherapy (Yes or not)

**PRIMARY OBJECTIVE:** To compare progression-free survival (PFS) of patients with advanced ovarian, primary peritoneal and Fallopian tube cancer when treated with Carboplatin-Paclitaxel-Bevacizumab vs Carboplatin-Paclitaxel-Bevacizumab-Rucaparib vs carboplatin-Paclitaxel-Rucaparib according to Homologous Recombination Deficient (HRD) status
HRD positive cohort
Randomization before starting chemotherapy

Comparison: Arm B (Carbo-Paclitaxel followed by Rucaparib) vs Arm C (Carbo-paclitaxel-beva followed by Rucaparib + Bevacizumab)
✓ HR: 0,65
✓ Alfa: 0,2 (1 tail)
✓ Beta: 80%
✓ N° of patients: assuming up to 30% patients achieve SD or PD during CHT 110 HRD patients will be enrolled
✓ Events: 62

HRD negative cohort

Comparison: Arm B (Rucaparib) and Arm C (Bevacizumab + Rucaparib) vs Arm A (Bevacizumab)
✓ HR: 0,7
✓ Alfa: 0,2 (1 tail)
✓ Beta: 80%
✓ N° of patients: 60 in each arm (180 overall)
✓ Events: 90
Operational information

- Amendment submitted to EC on 04/2020
- Contract negotiation: in progress
- HRD test: Foundatione One LOH test
- 30 italian centres
- Accrual rate: 30 months
- Trial duration: 5 years
CCTG-Led Trial Proposal

DOMINO:
Durvalumab as part of Post-Operative Therapy for Mismatch Repair-deficient Endometrial Cancer

Stephen Welch, MD, FRCPC
CCTG Endometrial WG Co-chair
Associate Professor, Oncology
Western University, London ON, Canada

Contact: stephen.welch@lhsc.on.ca
Resected stage III endometrioid endometrial cancer
LND mandatory**
Local d-MMR

Stratify by:
- ECOG PS
- CRT regimen

*Chemoradiotherapy = Investigators’ choice ("sandwich" vs PORTEC3)
**Sentinel LND allowed

CCTG Proposal:
Durvalumab as part of Post-Operative Therapy for MIsmatch Repair-deficient eNdOmetrial cancer (DOMINO)

1:1

Randomize

Durvalumab
1500 mg IV Q4W (max 12 months)

Observation

NED on CT

Sample size = 170 pts
Statistical consideration

• **Primary endpoint** = 3-year Failure-free survival rate
  • Assumption 3-year FFS rate = 75% for CRT (from PORTEC-3)
  • Powered to observe 15% difference (75 to 90%, power = 80%, \( \alpha = 0.1 \))
  • N= 78 per arm (including 9% lost to follow-up) = 170 pts

• **Secondary endpoints:**
  • OS, Safety, PRO, health-economic analysis
  • Correlative studies:
    • Tumour and ctDNA for genomics, PD-L1 IHC,
    • Obesity markers – serum leptin, IL-6, hs-CRP

• **Current status:**
  • Astra Zeneca interest ongoing
  • Final approval from CCTG Exec pending verification of international partnership
PHASE II COMMITTEE  
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Co-Chair: Alexandra Leary  
Harmonization Liaisons: XXX(Ops); Paul (Stats)  

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ENGOT-EN3 / NSGO-PALEO  

Mirza  
Mirza  
Mirza  
Mirza
A phase II study of Neoadjuvant chemotherapy plus TRemelimumab and Durvalumab in Advanced-stage ovarian cancer

Trial setting: ovarian cancer/front-line
Study Design: a phase II study
Participating Groups: KGOG, GCGS
Sponsor: Yonsei University College of Medicine
Status: Enrollment completed
Grant support: AstraZeneca
Drug supply: AstraZeneca

ESR-17-13142, NCT03899610, KCT0003742
KGOG 3046, TRU-D
Single arm phase II
Inclusion: stage IIIC & IV OVCA, Total n=24

**Neoadjuvant chemotherapy**
- Paclitaxel-Carboplatin Q3W
- Tremelimumab 75mg Q3W
- Durvalumab 1500mg Q3W

**Pre-treatment: Biopsy #1**
- Fresh frozen
- Immune marker analysis using FACS
- PD-L1 expression (SP263)
- Exome sequencing
- RNA sequencing

**Interval Debulking Surgery**

**Surgical specimen: Biopsy #2**
- Fresh frozen
- Immune marker analysis using FACS
- PD-L1 expression (SP263)
- Exome sequencing
- RNA sequencing

**Adjuvant chemotherapy**
- Paclitaxel-Carboplatin Q3W
- Durvalumab 1120mg Q3W (to C15 or PD)

**Post-treatment: Biopsy #3**
- Fresh frozen (optional)
- Immune marker analysis using FACS
- PD-L1 expression (SP263)
- Exome sequencing
- RNA sequencing

Primary endpoint: 12 months PFS rate
Secondary endpoint: PFS, OS, duration of response, pCR rate after NAC, CRS after NAC, R0 rate at IDS

After safety-run in, DSMB reviewed the safety and recommends the continuation of the study data (Jan 7th 2020).
Enrollment has been completed on Apr 9th 2020.
KGOG 3045 / AMBITION

An umbrella study of Biomarker-driven Targeted therapy In patients with platinum-resistant recurrent Ovarian cancer

Trial setting: Ovarian cancer/Recurrent/Heavily-treated
Study Design: Umbrella study
Participating Groups: KGOG, GCGS
Sponsor: Yonsei University College of Medicine
No. of already recruited patients: 40 patients were allocated to treatment
Status: Recruiting (First patient screened on Dec 2018)
Grant support: Severance Hospital Research Fund for Clinical Excellence
Drug supply: AstraZeneca

ESR-17-12678, NCT03699449, KCT0003283
Platinum-resistant Recurrent Ovarian Cancer After 2nd line of chemotherapy

Genomic Profiling

HRR gene panel

HRD+

Olaparib+ Cediranib

Arm 1

HRD-

PD-L1 expression by IHC

Random

Olaparib+ Durvalumab

Arm 2

PD-L1+

Durvalumab+ SOC

Arm 3

PD-L1-

Durvalumab+ Tremelimumab+ SOC

Arm 4

Durvalumab+ Tremelimumab (High) + SOC

Arm 5

Biomarker 1

Biomarker 2

Targeted agents

Primary endpoint: ORR
O+C or O+D is assumed with 30%
D+SOC or D+T+SOC is assumed with 25%
SOC, standard of care

Open: recruiting
Status: FPI in Dec 2018
Target: 86 pts

<table>
<thead>
<tr>
<th>Number</th>
<th>Gene Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BRCA1</td>
</tr>
<tr>
<td>2</td>
<td>BRCA2</td>
</tr>
<tr>
<td>3</td>
<td>ATM</td>
</tr>
<tr>
<td>4</td>
<td>BRIP1</td>
</tr>
<tr>
<td>5</td>
<td>PALB2</td>
</tr>
<tr>
<td>6</td>
<td>RAD51C</td>
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<td>7</td>
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<tr>
<td>12</td>
<td>PPP2R2A</td>
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<tr>
<td>13</td>
<td>RAD51B</td>
</tr>
<tr>
<td>14</td>
<td>RAD51D</td>
</tr>
<tr>
<td>15</td>
<td>RAD54L</td>
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</tbody>
</table>
ENGOT-OV30/NSGO-UMBRELLA - Trial Design

A phase II umbrella trial in patients with relapsed ovarian cancer

### Part 1

- **Cohort A**: n=25
  - MED19447 + Durvalumab
- **Cohort B**: n=25
  - ATR + Durvalumab
- **Cohort C**: n=25
  - “ATR+Durva+Olaparib” TBD

Treatment until disease progression

### Part 2

Evaluation of results of each cohort (both overall and with biomarker defined subgroups) to decide if it is feasible to proceed to part 2 for the given cohort

#### Part 2 Options:

- MED19447 + Durvalumab
- Standard of Care
- ATR + Durvalumab
- Standard of Care
- TBD
- Standard of Care

#### Randomization

2:1

**ENGOT model:** A
**Status:** Screening stopped for cohort A
**Protocol for cohort B in preparation**

**Sponsor:** NSGO-CTU
**NSGO-CTU PM:** Mette Engell

**Primary end-point:**
Disease control rate (DCR) (CR+PR+SD) at 16 weeks.

**COHORT A COMPLETED**
To be presented in 2021 with translational research endpoints
PHASE II COMMITTEE  
TUESDAY, MAY 26, 2020, 8:00 EDT; 14:00 CET  
Chair: Mansoor Mirza  
Co-Chair: Alexandra Leary  
Harmonization Liaisons: XXX(Ops); Paul (Stats)  

AGENDA  

Welcome & Introductions:  
COI declarations:  
Approval of Minutes/Report: November 2019 (posted on GCIG website)  
Motion: ________________________________ Seconded: _________________________  

New Concepts/Proposals (max 5 slides):  
KGOG OPEB-01  
KolGOTrIPIROC  
KolGOTrHIPEC-HR  
KGOG OPEB-01  
Jung-Yun Lee  
Asima Mukhopadhyay  
Asima Mukhopadhyay  

Update of Trials in Development (max 3 slides):  
MITO 25.1  
CCTG DOMINO  
Domenica Lorusso  
Stephen Welch  

Summary of ongoing trials without substantial new information (1 slide):  
KGOG 3046 TRU-D  
KGOG 3045  
ENGOT-OV30 / NSGO-Umbrella  
Jung-Yun Lee  
Jung-Yun Lee  
Mirza  

Closed for enrollement / Published Trials (1 slide):  
ENGOT-OV24 / NSGO-AVANOVA  
ENGOT-EN2 / NSGO  
ENGOT-EN1 / NSGO-FANDANGO  
ENGOT-EN3 / NSGO-PALEO  
Mirza  
Mirza  
Mirza  
Mirza
A phase I study to evaluate the safety and tolerability of bevacizumab-Niraparib combination therapy and determine the Recommended Phase 2 Dose (RP2D) in Women with platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer

**ENGOT-OV24/NSGO-AVANOVA1**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Bevacizumab Dose</th>
<th>Niraparib Dose</th>
<th># of Patients</th>
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</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>15mg/kg q 3 wks</td>
<td>100mg once daily</td>
<td>3</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>15mg/kg q 3 wks</td>
<td>200mg once daily</td>
<td>3</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>15mg/kg q 3 wks</td>
<td>300mg once daily</td>
<td>3</td>
</tr>
<tr>
<td>Cohort 4 (optional)</td>
<td>7.5mg/kg q 3 wks</td>
<td>300mg once daily</td>
<td>3</td>
</tr>
</tbody>
</table>

*Dose Escalation from cohorts 1 to 2 to 3 to 4*

- No Dose Limiting Toxicity: Escalate to cohort 2
- No Dose Limiting Toxicity: Escalate to cohort 3
- Bev related toxicity: Consider cohort 4

**ENGOT model:** A

**Sponsor:** NSGO-CTU

**NSGO-CTU lead PI:** Mansoor Mirza

**NSGO-CTU PM:** Nicole Buchner Vinum

**Status:** Randomization closed

**Last patient recruited:** 12-10-2015

**Recruitment:** 12 patients at Rigshospitalet, Copenhagen

**Primary endpoint:** Safety and tolerability

**Publication:** Mirza MR et al. Cancer Chemother Pharmacol 2019; 84:791-798
ENGOT-OV24/NSGO-AVANOVA2

A two-arm, open-label, phase II randomized study to evaluate the efficacy of niraparib versus niraparib-bevacizumab combination in women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

**Current status updated 30-04-2020**

| In treatment | 6 |
| End of treatment | 91/97 |
| 1st progression | 79/85A |
| In FU | 17 |
| 2nd progression | 55/71B |
| End of study | 60/97 |
| OS | 58 |

A: 12 pts got new anti-cancer therapy or had EOS before 1st progression
B: 26 pts had EOS before 2nd progression

**ENGOT model:** A
**Sponsor:** NSGO-CTU
**NSGO-CTU lead PI:** Mansoor Mirza
**NSGO-CTU PM:** Nicole Buchner Vinum
**Total number randomised:** 103
  - Arm B+C: 97
  - Arm A: 6

**Primary endpoint:** Progression-free survival (PFS)
**Publication:** Mirza MR et al. Lancet Oncol 2019; 20: 1409-1419

**Gynecologic Cancer**

**Session Type:** Poster Discussion Session

**Date and Time:** 05/29/2020, 8:00 AM - 11:00 AM; 05/29/2020, 8:00 AM - 11:00 AM

**Role Responsibilities:** Presenter

**Abstract Title:** Final survival analysis of NSGO-AVANOVA2/ENGOT-OV24: Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: “A randomized controlled chemotherapy-free study.”

**Abstract ID:** 6012

**Primary endpoint: PFS in the ITT population**

Adjusted HR = 0.35 (95% CI 0.21–0.57) p<0.0001

Updated PFS; TFST; TSST; PFS2; OS

Gynecologic Cancer

Session Type: Poster Discussion Session

Date and Time: 05/29/2020, 8:00 AM - 11:00 AM; 05/29/2020, 8:00 AM - 11:00 AM

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Abstract ID: 6012
A phase II Trial of postoperative chemotherapy or no further treatment for patients with node-negative stage I-II intermediate or high-risk endometrial cancer.

**Chemotherapy**
- Carboplatin-Paclitaxel x 6
- + Brachytherapy

**Observation**
- + Brachytherapy

**Primary end-point:** Overall survival (OS)

**Primary Endpoint (OS) expected:** 2022/2023

**n=240**

**Engot model:**
- Status: Randomization closed
- Last patient randomized: 23.04.2019
- Sponsor: DGCG
- NSGO-CTU PM: Joan Lohndorf

**Supported by**
- Danish Cancer Society
- EORTC
ENGOT-EN1/FANDANGO - Trial Design

A randomised double-blind placebo-controlled phase II trial of first line combination chemo-therapy with Nintedanib/placebo for patients with advanced or recurrent endometrial cancer.

Stratification:
- Stage of disease (stage 3C 2 vs. stage 4 vs. recurrent disease)
- Prior adjuvant chemotherapy (yes/no)
- Disease status (Measurable vs. non-measurable disease according to RECIST 1.1)

Primary Endpoint (PFS) expected: 2021
ENGOT-EN3/NSGO-PALEO - Trial Design

A randomized, double-blind, placebo-controlled, phase II trial of Palbociclib in combination with Letrozole versus Placebo in combination with Letrozole for patients with Estrogen Receptor Positive advanced or recurrent Endometrial cancer.

**Endometrial Cancer**
- Primary stage 4 or relapsed disease
- ER positive endometrioid adenocarcinoma

**Randomization:**
- 1:1
- N=78

**ARM A**
- Letrozole, 2.5mg d 1-28 every 28 days
- Placebo 125mg d 1-21 every 28 days
- Until progression

**ARM B**
- Letrozole, 2.5mg d 1-28 every 28 days
- Palbociclib 125mg d 1-21 every 28 days
- Until progression

**Stratification:**
- Number of prior lines (primary adv disease vs. 1st relapse vs. ≥2 relapses)
- Measurable vs. evaluable disease
- Prior use of MPA/Megace

**ENGOT model:**
- **Status:** Randomization closed
- **Last patient randomized:** 21.12.2018
- **Sponsor:** NSGO-CTU
- **NSGO-CTU PM:** Joan Løhndorf

**Primary end-point:**
- Progression-Free Survival (PFS)

**Primary Endpoint (PFS):**
- ESMO 2020
Thank You!