

NCRI Gynaecological Cancer Clinical Studies Group

Introduction

The last 12 months has seen steady activity with ICON7-7 closing and PORTEC3 finally opening after lengthy delays. We have worked to develop a Phase II Network for cancer of the cervix and a similar model for cancer of the ovary.

Membership and structure

A number of members have stepped down. These include Professors Gordon Jayson, Gordon Rustin and Sean Kehoe, Drs John Green and Philip Burn and Ms Pamela Morton of Jo's Trust. The Group is very grateful for the work, commitment and expertise that these former members contributed.

New members to join included Dr Andrew Clamp (Medical Oncologist), Dr Anna Montes (Medical Oncologist) and Sundha Sundar (Gynaecological Oncologist). Professor Glen McCluggage from the British Association of Gynaecological Pathologists and Dr Dearbhaile O'Donnell from the ICORG have been co-opted onto the Group. Andrea Harkin our Portfolio Co-ordinator resigned and Gemma Tait was appointed as a Project Officer on the basis of six hours per week.

The Endometrial Subgroup met on one occasion and had a teleconference on another. The Cervix Subgroup met on one occasion and the Ovarian Subgroup met on two occasions. The Chairs of the Subgroups were unchanged during the year. Gemma Tait has been working as Project Officer with two principal goals. The first is to establish a phase II network to speed up our accrual into phase II studies, particularly cervix and the other is to try to establish closer collaboration with the clinical collaborators in the Cancer Networks. There has been a general reduction in the number of active Research Networks with a higher proportion of accrual coming from a lower proportion of Networks and we wish to improve our communication with these Networks.

Portfolio and accrual

Table 1 contains the current Gynaecological Cancer CSG portfolio.

Table 1: Gynaecological Cancer CSG portfolio

Acronym	Title	PI(s)	Status
ARTISTIC	A Randomised Trial In Screening To Improve Cytology	Professor Henry Kitchener	Closed
ASTEC	A randomised trial of lymphadenectomy and of adjuvant external beam radiotherapy in the treatment of endometrial cancer	Professor Henry Kitchener	Closed
BIBF1120	A randomised placebo-controlled phase II study of continuous maintenance treatment with BIBF 1120 following chemotherapy in patients with relapsed ovarian cancer	Professor Jonathan Ledermann	Closed
CA125 Doubling Time	Use of changes in CA 125 doubling time to detect activity of cytostatic agents in women relapsing with ovarian carcinoma. Study 1 - tamoxifen	Professor Gordon Rustin	Open
Care-in-Chemo (C-in-C)	Home versus hospital day case delivery of chemotherapy for advanced breast or	Professor Hilary Thomas	Closed

	ovarian cancer: Health-related quality of life, costs and family acceptability.		
CCC-1 (JGOG 3017/GCIG)	Randomized Phase III Trial of Paclitaxel plus Carboplatin (TC) Therapy versus Irinotecan plus Cisplatin (CPT-P) Therapy as a First Line Chemotherapy for Clear Cell Carcinoma of the Ovary	Professor John Green	In set up
Cervical screening among Eastern European migrants	Understanding cervical screening participation among women immigrants from Eastern Europe	Professor Jane Wardle	Open
CHORUS (feasibility)	A randomised feasibility trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal, or fallopian tube carcinoma	Professor Sean Kehoe	Open
CHORUS	CHemotherapy OR Upfront Surgery A randomised feasibility trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal, or fallopian tube carcinoma	Professor Sean Kehoe	Open
CRISP-1	(Cervical Randomised Intervention Study Protocol) An investigation into the effects of diindolylmethane (BioResponseDIM) supplementation in women with low-grade cervical cytological abnormalities.	Professor Alison Fiander Professor Peter Sasieni	Closed
CTCR-CE 01	Dynamic contrast enhanced MRI in combination with tumour molecular profiling as predictors of radiation response in cervix cancer	Dr Li Tee Tan	Open
CTCR-OV01	Expression profiling of advanced epithelial ovarian cancer to predict chemotherapy response study	Dr James Brenton	Closed
CxII	Phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer.	Dr Mary McCormack, Professor Jonathan Ledermann	Open
DCE-MRI	Dynamic contrast enhanced MRI measurement of tissue perfusion in cancer patients	Mr Andrew Jones	Open
Decitabine and Carboplatin in Relapsed Ovarian Cancer	A Cancer Research UK randomised phase II Trial of the DNA-hypomethylating agent, 5-Aza-2'-deoxycytidine (Decitabine) given intravenously in combination with carboplatin, versus carboplatin alone given 4 weekly in Patients with	Professor Stanley Kaye	Closed

	progressive ovarian cancer.		
DNA Methylation Study	DNA methylation as a predictor for response and progression free survival in patients with ovarian cancer	Dr Nadeem Siddiqui	Open
Early Relapsed Ovarian Cancer	Phase II study of carboplatin and gemcitabine chemotherapy in patients with advanced ovarian cancer resistant or refractory to previous platinum chemotherapy	Dr Mary McCormack Professor Jonathan Ledermann	Closed
EMBRACE	Epidemiological study of BRCA1 and BRCA2 mutation carriers	Professor Douglas Easton	Open
EORTC 55963	Phase III randomized study of chemotherapy with or without secondary cytoreductive surgery in patients with recurrent ovarian epithelial cancer	M.E.L. Van Der Burg, G. Favalli	Closed
EORTC 55971	Phase III randomized study of neoadjuvant chemotherapy followed by interval debulking surgery versus upfront cytoreductive surgery followed by chemotherapy with or without interval debulking surgery in patients with stage IIIC or IV ovarian epithelial, peritoneal, or fallopian tube cancer	Dr Sergio Pecorelli, Professor Gordon Rustin, Ignace Vergote	Closed
EORTC 55984	Phase III randomized study of doxorubicin and cisplatin with or without paclitaxel in patients with locally advanced, metastatic, and/or relapsed endometrial cancer.	Dr Nicholas Reed	Closed
EORTC 55985	Phase II clinical trial on Taxol as single agent in locally advanced and/or metastatic or recurrent vulva cancer not amenable for surgery and/or radiotherapy - EORTC trial 55985	Professor John Green	Closed
EORTC 55991	Phase II randomised study of adjuvant radiation with or without chemo in high risk endometrial carcinoma	Carlos Freire de Oliveira, Gunnar B Kristensen, Dr Nicholas Reed	Closed
GEM/TREO	A phase II trial of gemcitabine and treosulfan in patients with advanced carcinoma of the ovary.	Professor Hilary Thomas	Closed
GROINSS-V II	GRONingen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) II	Mr Peter Baldwin	Open
HIDOC-EIS	A Randomised Phase III Trial of sequential High Dose Chemotherapy or Standard Dose Chemotherapy for Optimally Debulked FIGO Stage III and IV Ovarian Cancer.	Professor Jonathan Ledermann	Closed
HOT II	Randomised double-blind controlled phase III trial of hyperbaric oxygen therapy in patients suffering long-term adverse effects of radiotherapy for	Professor John Yarnold	Open

	pelvic cancer		
ICON4	A randomised trial of paclitaxel (Taxol) in combination with platinum chemotherapy versus conventional platinum-based chemotherapy in the treatment of women with relapsed ovarian cancer	Professor Jonathon Ledermann	Closed
ICON5	An international, 5-arm randomised trial of paclitaxel and carboplatin v triplet or sequential doublet combinations in patients with epithelial ovarian or primary peritoneal carcinoma.	Dr Peter Harper	Closed
ICON6	A randomised trial of AZD2171 in combination with platinum-based chemotherapy in ovarian cancer relapsing more than 6 months following completion of first-line platinum-based treatment	Dr Clair Amos	Open
ICON7	A randomised, two-arm, multicentre gynaecologic cancer inter-group trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer	Dr Timothy Perren	Closed
MAVARIC	Manual Assessment Versus Automated Reading In Cytology	Professor Henry Kitchener	Open
mEOC	A GCIG Intergroup multicentre trial of open label carboplatin and paclitaxel +/- bevacizumab compared with oxaliplatin and capecitabine +/- bevacizumab as first line chemotherapy in patients with mucinous Epithelial Ovarian Cancer	Professor Martin Gore	In set up
MRC OV07/EORTC 55041	A randomised, multicentre, phase III study of erlotinib versus observation in patients with no evidence of disease progression after first line platinum-based chemotherapy in high-risk stage I and stage II-IV epithelial ovarian, primary peritoneal and fallopian tube cancer.	Dr Marcia Hall	Closed
NCRN065	Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens	Professor Jonathan Ledermann	Open
NCRN068 -	NCRN068 - INDUSTRY STUDY	Professor Hilary Calvert	In set up
NCRN086	NCRN086 - INDUSTRY STUDY		
NEO-ESCAPE	A randomised feasibility study of extended chemotherapy with neoadjuvant carboplatin followed by adjuvant paclitaxel and gemcitabine vs.	Dr Christopher Poole	Open

	gemcitabine and carboplatin followed by paclitaxel alone, in patients with advanced epithelial ovarian		
NSECG	National study of endometrial cancer genetics	Professor Ian Tomlinson	Open
OV05	A randomised trial in relapsed ovarian cancer: early treatment based on CA 125 levels alone versus delayed treatment based on conventional clinical indicators.	Professor Gordon Rustin	Closed
PARP BRCA Trial	A Cancer Research UK Phase II Proof of Principle Trial of the activity of the intravenous PARP-1 inhibitor, AG-014699, in known carriers of a BRCA 1 or BRCA 2 mutation with locally advanced or metastatic breast or advanced ovarian cancer	Dr Ruth Plummer	Open
POET	Prevention Of Endometrial Tumours	Professor Shirley Hodgson	Open
PORTEC3	Randomized Phase III Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy with Pelvic Radiation Alone in High Risk and Advanced Stage Endometrial Carcinoma: PORTEC-3	Dr Melanie Powell	Open
RAACS	Rural Accessibility And Cancer Survival	Dr Andy Jones	Closed
PRECIOUS	Improving the assessment and recording of cancer treatment effects	Dr Susan Davidson	Open
RT3VIN	A Randomised Trial of Topical Treatment in Women with Vulval Intraepithelial Neoplasia	Professor Alison Fiander	In Set-up
SCOTCERV	A phase II study of docetaxel and gemcitabine as second line chemotherapy in cervical cancer	Dr Paul Symonds	Closed
SCOTROC 4	A prospective multicentre randomised trial of carboplatin flat dosing vs inpatient dose escalation in first line chemotherapy of ovarian, fallopian tube and primary peritoneal cancers.	Professor Stanley Kaye	Open
SCOTROC 5	A feasibility study of sequential carboplatin followed by paclitaxel / gemcitabine as first-line chemotherapy for stage IC-IV ovarian, fallopian tube and primary peritoneal carcinomas	Professor Stanley Kaye	Closed
Self-sampling in non-responders for cervical screening	The potential role of self-sampling in women who do not attend for cervical screening – a randomised controlled trial	Dr Anne Szarewski	In set up
UK FOCSS	United Kingdom Familial Ovarian Cancer Screening Study	Professor Ian Jacobs	Open
UKCTC -207	A phase Ib/ II trial of CA4P (combretastin A-4 phosphate) in combination with carboplatin and	Professor Gordon Rustin	Open

	paclitaxel chemotherapy in patients with advanced cancer and advanced ovarian carcinoma		
UKCTOCS	The UK collaborative trial of ovarian cancer screening	Professor Ian Jacobs	Closed
UKFOCSS	The UK Familial Ovarian Cancer Screening Study	Dr James Mackay	Open

1114 patients were recruited to studies in 2008/9 representing 7.3% of incidence case. 539 patients (3.5% of incidence cases) were recruited to RCTs and 575 (3.8%) to non RCTs.

Trials which have closed include CXII, CRISP-1, ICON-7, MAVARIC, SCOTCERV and SCOTROC-4. The POET trial was stopped following a recommendation by the Trial Steering Committee.

New trials which have opened include PORTEC-3 and PETROC is in set-up along with the clear cell trial, CCC-1 (led by JGOG) and MEOC (collaboration between NCRI and GOG). As stated before, there has been awareness of falling accrual and we are trying to address this.

Trials in development

Following the closure of ICON-7, attention has turned to the next flagship ovarian cancer trial, which will be ICON-8. An outline has been submitted to CTAAC and the trial is likely to involve a number of arms, which will factor in 'dose dense' chemotherapy, both taxol and carboplatin, as well as the earliest available results from ICON-7 when they are available (probably May/June 2010), relating to the efficacy of bevacizumab. Following the initiative between the NCRN and AstraZeneca (AZ) to make available the latter's phase II pipeline drugs for NCRN trials, the Group has been successful in a proposal to use the anti-VEGF drug cediranib (Recentin), in a randomised phase II trial in recurrent cervical cancer. This trial will be known as CIRCCa and is expected to open in January 2010. This will have a related translational component. The P for the study is Dr Paul Symonds.

A further similar proposal using the drug AZD0530, has been resubmitted to CTACC. This is another anti-angiogenic drug and is being proposed as a randomised phase II with platinum based chemotherapy in recurrent ovarian cancer. After a recent meeting between AZ and the NCRI Groups, there is the potential to develop yet another phase II, this time in endometrial cancer, incorporating Recentin. This will be further explored and may develop into an application to CTAAC.

Meetings

A very successful Ovarian Subgroup meeting was held in Glasgow, which attracted around 100 people. This allowed the opportunity to discuss the entire ovarian portfolio.

Collaborations

The NCRI Gynae CSG is an active participant in the Gynecological Cancer InterGroup. Professor Henry Kitchener became its Chair in November 2008 and Professor Jonathan Ledermann joined its Executive Board. Professor Iain McNeish is the Co-Chair of the Translational Working Party. The NCRI leads two international collaborative trials through the GCIG, ICON-6 and ICON-7, and it is a collaborating Group in CCC-1. As stated above, it will lead with the GOG the MEOC trial of cytotoxic chemotherapy and bevacizumab in mucinous adenocarcinoma of the ovary.

Other activities

The Group hosted a Cervical Cancer State of the Science meeting, which was held in Manchester on 18/19 June. This was a collaboration between the NCI, NCRI and GCIG. The meeting brought together 65 delegates from 20 countries with the goal of developing new concepts for cervical cancer trials. This was a very successful meeting and international collaborative trials should take root as a consequence. One of the core themes was that most cervical cancer worldwide occurs in low/middle income countries and there were seven or eight centres of excellence from such countries represented. Enthusiasm to participate by these centres could translate into greatly enhanced accrual into international collaborative trials.

The Group was involved in advising on a NICE scoping exercise in relation to the development of clinical guidance in ovarian cancer.

Three year strategy

Our strategy is really based on the outcome of the three year progress report from 2007. We have not held any strategic meetings the past year.

Priorities for next year

Our priorities include

- the establishment of a new flagship ovarian cancer trial,
- to get PORTEC-3 recruiting for as many centres as possible in order to provide a major contribution to this important trial,
- we wish to increase our accrual across the portfolio and in particular, we wish to see the phase II cervix network bearing fruit with rapid completion of the CIRCCa study following its opening in January 2010 and
- a final priority will be to make progress in developing an international phase III cervix trial, which would probably involve either additional chemotherapy following standard chemoradiation or new adjuvant chemotherapy followed by chemoradiation in the light of the results of the CxII phase II trial.

Professor Henry Kitchener, Chair

Appendix 1

2008/09 Publications & abstracts

This has been a good year for reporting our trials, with the ASTEC trial being reported in two papers in the Lancet and the ARTISTIC trial being reported in Lancet Oncology and ICON-5 was reported in the Journal of Clinical Oncology. The NCRI Group feature prominently at ASCO this year; OVO-5, which compares the value of CA125 relapse compared with clinical relapse as the starting point for second line chemotherapy, featured in the plenary session at ASCO, indicating the importance of this study. There were also oral presentations at ASCO for the BIBF study as well as the Combrestatin study, and CxII and SCOTROC-4 were reported as Posters.

Professor Jonathan Ledermann, who chairs our Ovarian Subgroup, was a discussant for the gynaecological oral session.

Published Papers

ASTEC Writing Committee on behalf of the ASTEC EN.5 Study Group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*, 2009; **373**:125-36.

ASTEC Writing Committee on behalf of the ASTEC EN.5 Study Group. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (VRS ASTEC and NCIC CTG EN5 randomised trials): pooled trial results, systematic review and meta-analysis. *Lancet*, 2009; **373**:137-46.

Kitchener HC, Almonte M, Thomson, C Wheeler P et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncology*, 2009; published on-line June 18th.

ICON-5 (details TBA)