

NCRI Gynaecological Cancer Clinical Studies Group

5 members left the Group and 8 new members were appointed. Dr Jo Davis from the Scottish Gynae Trials Group was invited as an observer and Dr Terry Rollason who chairs the British Association of Gynaecological Pathology also now attends as a full member of the Group.

Subgroups

A new subgroup has been formed, the Prevention and Screening Subgroup, which held its initial meeting on May 18th. There is already a very strong portfolio of screening trials and although there are already two prevention studies, there is scope for strengthening this aspect of the portfolio.

Portfolio and accrual

ICON5, which closed in late 2004, had its first primary analysis presented as a late breaking abstract at ASCO in June 2006.

ASTEC, which closed in the second quarter of 2005, underwent a primary analysis of the surgical component and found that lymphadenectomy had no impact on overall survival. This has important implications for the future role of lymphadenectomy worldwide. The results were presented in plenary at the European Society for Gynaecological Oncology in September 2005 and won the prize for the best paper. It was also presented in plenary at the Society for Gynaecological Oncology in the USA in March 2006. The manuscript is to be submitted to the Lancet within the next 2-3 months. The analysis on radiotherapy randomisation within ASTEC requires further events and is not going to be possible until 2007.

The past twelve months has been spent largely on developing new trials. No new trials opened, other than two "local" phase II studies. This development phase has now come to fruition with a number of newly funded randomised trials, two of which will have major international participation led by the NCRI; ICON6 and ICON7. Another trial, POET, launched in June is an endometrial cancer prevention trial. A successful trials meeting was held in London in September 2005. The ASTEC results were presented and the rest of the portfolio going forward was presented and discussed.

Current activity within the tumour specific areas is as follows:

Ovarian Cancer

A randomised trial of erlotinib (Tarceva) as a maintenance treatment following primary treatment for ovarian cancer has been delayed in its onset for a number of reasons. There had been a delay in getting a final protocol for submission to CTAAC and then some delays in international agreements as this is being led by the EORTC. This trial should open soon in the UK.

ICON7, which is being launched in June, will randomise women with ovarian cancer to carboplatin/paclitaxel or carboplatin/paclitaxel + Avastin. ICON7 will be an InterGroup trial with the NCRI leading.

ICON 6 will also launch later this year and is a very innovative randomised trial of molecular targeted agents in combination with platinum based chemotherapy for platinum sensitive recurrent disease. ICON 6 will also be an InterGroup trial with the NCRI leading.

OVO5 has closed to recruitment and is now waiting sufficient relapse events in order to be able to complete.

SCOTROC4 is recruiting satisfactorily.

CHORUS has completed a feasibility study and following this, a decision was made to continue on into a definitive phase III trial.

An important development in the past twelve months has been publication of the US trial GOG172, which indicated the superior therapeutic effect of intraperitoneal chemotherapy in ovarian cancer. An NCI clinical announcement was made based on a systematic review, recommending the use of this modality of treatment. It is now important that we develop feasible protocols as the toxicity in GOG172 was considered excessive. As a result, the NCRI have submitted a randomised phase II to the newly formed Feasibility Committee, proposing a randomised phase II of paclitaxel IV + carboplatin IP versus paclitaxel IV/IP + carboplatin IV.

Endometrial Cancer

As outlined above ASTEC has closed and the Group has just agreed to join PORTEC3. This is a randomised trial of chemoradiation plus chemotherapy for high-risk endometrial cancer. This is seen to be the area where we should have a frontline trial and an InterGroup with PORTEC, who have an excellent track record, should be a strong basis for a trial that will require collaboration. The PORTEC3 protocol has been reviewed in Holland and funded by the Dutch Cancer Society. Following a survey of clinical oncologists to confirm support, a full outline of PORTEC3 will be submitted to CTAAC. PORTEC will be the lead group.

The POET trial, which has been funded by CTAAC, will launch in June. It randomises HNPPC women who have a strong predisposition to endometrial cancer to surveillance or to insertion of an intrauterine progestogen device (Mirena). The objective of the trial is prevention of severe atypical hyperplasia and endometrial cancer.

An outline of an Australian protocol has been approved by CTAAC to go for full proposal, which will compare laparoscopic and open surgery for endometrial cancer. This would be the first randomised trial of total laparoscopic hysterectomy, which differs from the technique used in the GOG lap 2 trial. Again NCRI would not be the lead group but this type of trial requires international collaboration. Alan Farthing will be the UK lead investigator.

Cervical Cancer

There are currently two phase II cervical cancer trials in progress. SCOTCERV is a phase II trial of docetaxel and gemcitabine in relapsed cervical cancer and the other is CxII which uses neoadjuvant chemotherapy prior to radical chemoradiation for locally advanced cervical cancer. This will be useful in determining an experimental arm for an overdue randomised trial in advanced cervical cancer, for which international collaboration will be required.

Vulval Cancer

There are no randomised trials for treatment of vulval cancer being planned. A Dutch protocol which involves the use of sentinel groin node detection to determine the use of radiotherapy rather than full groin dissection (GROINS V) is being adopted by a number of investigators in the UK and an MREC application is current. This will offer the opportunity to broaden experience in this important development. An application for

formal funding is being considered. Standardised radiological and radiotherapy protocols will need to be developed.

A phase II study of pressure stockings to prevent lymphoedema is currently being undertaken at Gateshead.

Translational Research

This is led by the Translational Subgroup. SCOTROC5 is in progress and a proposal in conjunction with ICON7 is currently with TRICC, as well as other proposals to support trials in endometrial cancer currently being considered by CTAAC.

Existing translational studies in ovarian cancer comprise a single centre study using the Affymetrix platform to explore gene expression in the response to paclitaxel or platinum in the randomised phase 2 setting, and a larger multiplatform study based round SCOTROC4 where gene expression, DNA copy number and methylation profiling will be carried out on both solid tumour and ascites specimens assessing the response to platinum agents. This year an outline application has been submitted to TRICC for a large international study (ICON7) to determine the predictive value of proteomic patterns in assessing response to first line chemotherapy. ICON7 evaluates the addition of the angiogenesis inhibitor bevacizumab to cytotoxic chemotherapy in ovarian cancer and will also assess relevant immunohistochemical markers such as VEGF2 on outcome.

The Subgroup has developed a working relationship with Oncore and has submitted an outline collection proposal on the InterGroup study OVO7 which will require working closely with the tissue bank as it evolves from its pilot phase and incorporates an increasing number of UK centres. In OVO7 paraffin blocks and serum/plasma samples will be collected with monitoring of quality control in storage, collection and data linkage.

During the past year accrual to trials dipped to 3.5% compared with 5.4% and 5.2% for 04/05 and 03/04 respectively. This was due to trials closing and the development of new trials not yet open. It is however, noteworthy that 9 cancer networks recruited fewer than 5 patients and this merits attention.

Other activities

The NCRI Gynaecological Studies Group continues to play an active and leading role in the Gynaecological Cancer InterGroup with 14 other international trials groups. We see international trial participation and development as a key role of our group. An illustration of this is the Endometrial Cancer 'State of the Science' meeting to be held in Manchester in November 2006, where 60 or 70 key international people will meet to develop the way forward for endometrial cancer trials. The NCI will bring around 30 experts from the United States to this event, which will have other representatives from around the world. This is being co-sponsored by the NCRI/NCRN and NCI.

Three-Year Strategic Plan

1. The question of succession was considered by the Group, prior to rotating its membership in June. Careful consideration was given to ensure both continuity in what is a well functioning group and new members with fresh thinking and energy.

The Chair was reappointed in June with the full support of the Group and subgroup chairs. Two subgroup chairs stood down from the main group (Tito Lopes and Peter Blake). They will be replaced as subgroup chairs from the main group. Gordon Rustin has agreed to continue for another year as Ovary Subgroup Chair and we will have strong candidates to replace him when he steps down as the subgroup chair. Henry Kitchener will be replaced as Endometrial Subgroup Chair.

2. The establishment of the Screening and Prevention Subgroup offers an opportunity to develop. We have a strong portfolio in screening but there is scope for strengthening prevention trials of which we now have two. These are not easy to do but are increasingly important.
3. We wish to acquire some psychosocial expertise on the Group, to be better placed to get more patient centred research funded, and will seek to coopt a member from the Psychosocial Oncology Clinical Studies Development Group. We should strengthen the psychosocial/quality of life outcomes in our clinical trials and undertake the type of patient centred research, which is strongly supported by our consumer representatives.
4. We will see translational research outputs coming through and we now have some very innovative trials to support future work, for example ICON 7. We have a strong Translational Subgroup and our applications to TRICC will increase.

We would benefit from a strong tissue bank to support translational research, and while there will be disparate collections on the back of different initiatives e.g. UKCTOCS, SCOTROC 4, ICON 3 and ICON 7 it would be desirable to try to get these more coordinated, in order to support larger studies.

5. As outlined in the site specific section, we are planning a number of submissions in the next 6-12 months and these are increasing opportunities for trials of biological agents both nationally and internationally.

The NCRI Gynaecological Clinical Studies Group is increasingly being seen internationally as a strong group to lead trials.

I wish to thank the Subgroup Chairs, in particular for their commitment and leadership and all the members for their contribution. I would also thank the MRC Cancer Trials office staff, especially Max Parmar, Ann Marie Swart and the Trial Managers for the expertise and commitment to the Gynae CSG.

Gynaecological Cancer Group Portfolio

Acronym	Title	PI(s)	Status
ARTISTIC	A Randomised Trial In Screening To Improve Cytology	Professor Henry C Kitchener	Closed
ASTEAC	A Randomised Trial of Lymphadenectomy and of adjuvant External beam Radiotherapy in the Treatment of Endometrial Cancer	Professor Henry C 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	Dr Jonathan Ledermann	Open
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 ovarian cancer: Health-related quality of life, costs and family acceptability.	Professor Hilary Thomas	Closed
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	Open
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 JD Brenton	Closed
CxII	Phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer.	Mary McCormack, Dr Jonathan Ledermann	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 Progressive Ovarian Cancer.	Prof Stanley Kaye	In Set-up
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	Dr Jonathan Ledermann	Closed

	chemotherapy		
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	Open
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	Open
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 A Green	Open
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	Open
GEM/TREO	A Phase II Trial of Gemcitabine and Treosulfan in patients with advanced carcinoma of the ovary.	Professor Hilary Thomas	Closed
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	Dr J Ledermann	Closed
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	Dr J 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
ICON7	A randomised, two-arm, multicentre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel)	Dr Timothy Perren	in Set-up

	in patients with epithelial ovarian cancer		
MAVARIC	Manual Assessment versus Automated Reading in Cytology	Professor Henry Kitchener	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	in Set-up
NEO-ESCAPE	A randomised feasibility study of extended chemotherapy with neoadjuvant carboplatin followed by adjuvant paclitaxel and gemcitabine vs. gemcitabine and carboplatin followed by paclitaxel alone, in patients with advanced epithelial ovarian	Dr Christopher Poole	in Set-up
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
POET	Prevention of Endometrial Tumours	Professor Shirley Hodgson	in Set-up
SCOTCERV	A Phase II Study of Docetaxel and Gemcitabine as Second Line Chemotherapy in Cervical Cancer	Dr Paul Symonds	Open
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.		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		Open
UKCTOCS	The UK collaborative trial of ovarian cancer screening	Professor Ian Jacobs	Open
UKFOCSS	The UK Familial Ovarian Cancer Screening Study	Dr James Mackay	Open

Professor Henry Kitchener, Chair