NCRI
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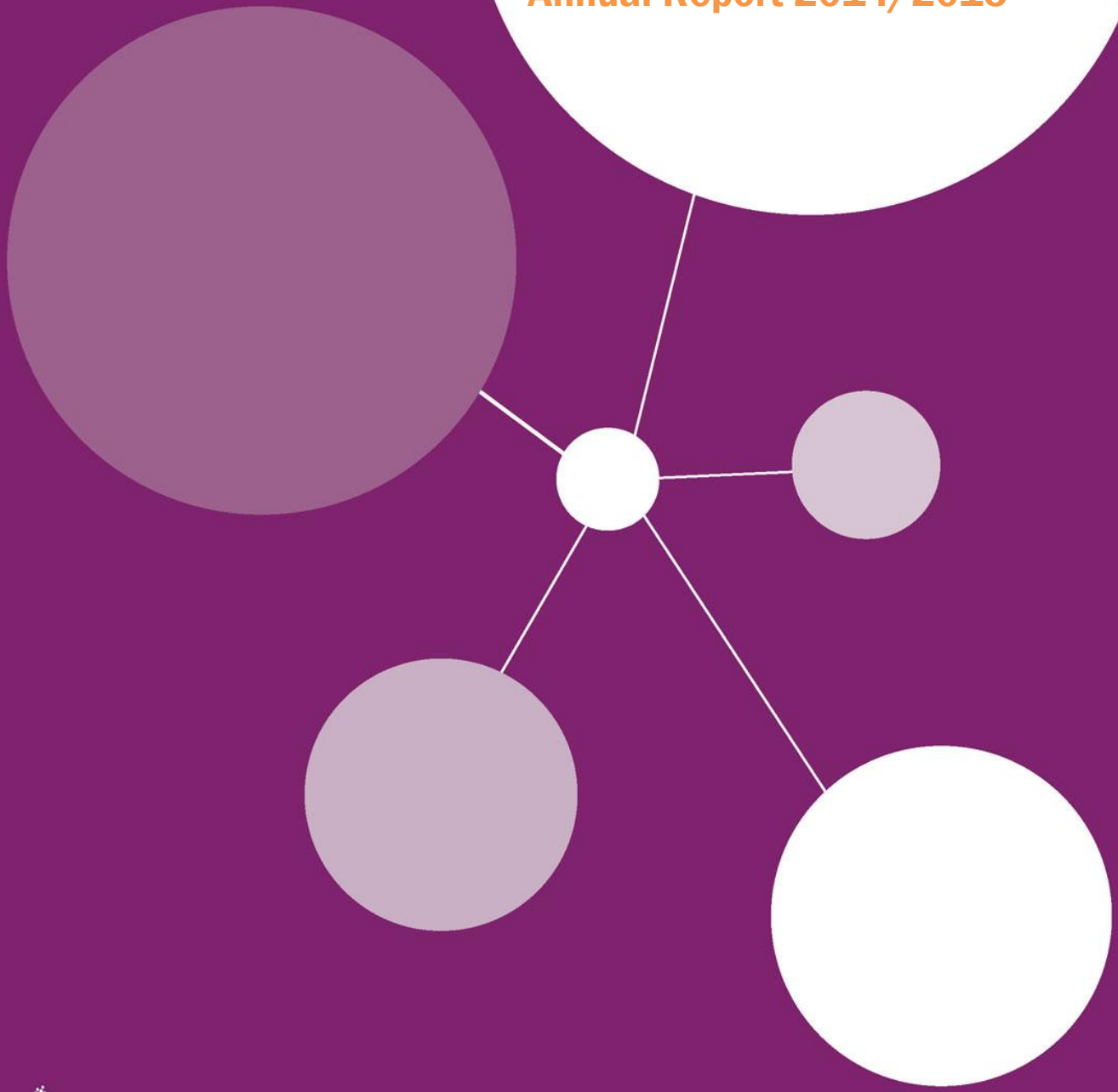
NCRI Gynaecological Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Gynaecological Cancer CSG
Annual Report 2014/15

1. Executive Summary (including top 3 achievements in the year)

Although gynaecological cancers comprise diseases in four distinct areas (ovary, endometrium, cervix and vulva), it is now clear that differences in biology and clinical behaviour exist within subtypes of all these groups. Future trials will require greater national and international cooperation and co-ordination and individual centres may recruit only a small number of patients. The NCRI Gynaecological Cancer Clinical Studies Group (Gynae CSG) has a long history of leading and recruiting to academically-driven trials that have changed practice. By the end of 2015, we will lead flagship international studies in all three major gynaecological disease areas. The research led by our group has been presented at major international meetings and is published in high-impact journals.

Many clinical trials of novel agents are directed by industry, but historically the UK has had a good record of collaboration, influencing the design, and providing leadership and good recruitment. The national strategic partnerships with industry help us to continue this. However, there are now excellent European Networks that can work flexibly with industry and the UK needs to ensure that our national structures and processes allow us to remain competitive and influential. Patient access to large-scale trials is rarely an issue. However, in many commercial trials, especially in specific subtypes of gynaecological cancer, access to novel drugs is often only available to a few centres.

Highlights of this year included the completion, in November 2014, of recruitment into ICON8, a large international trial in ovarian cancer. Moreover, its successor, ICON8B, will open in 2015. We have also recently opened NiCCC, the first UK's first trial specifically dedicated to ovarian clear cell carcinoma. We lead INTERLACE, an international trial in cervical cancer, providing an opportunity to improve outcome in this disease not only by introducing a new treatment, but also through better quality control of radiotherapy. The CSG also participates in SHAPE, a trial of simple versus radical surgery in early cervix cancer. The CSG will also open STATEC, a new international surgical trial in endometrial cancer, in 2016. Thus, with large-scale studies in each major disease area, we will remain an internationally competitive group.

2. Structure of the Group

The main structure of the Group has not altered during 2014 – 2015 with three subgroups (ovarian, endometrium and cervix/vulva) based upon primary disease site. Professor Iain

McNeish took over as Chair of the CSG in May 2014 and Dr Ros Glasspool became chair Ovarian Subgroup. The chairs of the Endometrium (Professor Richard Edmondson) and Cervix/Vulva (Professor Nick Reed) Subgroups remain unchanged. However, Dr Emma Hudson will take over as chair of the Cervix/Vulva Subgroup in late 2015. Subgroups continue to meet 2-3 times per year, usually once or twice face to face. The Endometrium and Cervix/Vulva Subgroups held a productive joint meeting in April 2015, and the Ovarian Subgroup continues to have its annual meeting with the Scottish Gynaecological Cancer Group in Glasgow in February. There will be another CSG clinical trials meeting in London in December 2015.

As with other CSGs, the Gynaecological CSG welcomed its first two trainee members in 2014 – Drs Debra Josephs and Michelle Mackintosh. There were over 30 applications for these posts, suggesting a wide enthusiasm for clinical trials amongst trainees in the three main specialties (medical oncology, clinical oncology, gynaecological oncology).

3. CSG & Subgroup strategies

Main CSG

The over-arching strategy of the Gynae CSG is to co-ordinate a portfolio of clinical trials that will collectively permit innovative and practice-changing research in gynaecological cancers. These trials will cover the spectrum of gynaecological malignancies and will be available to women throughout the UK. At the recent strategy meeting for the CSG, the three key priorities for the coming five years were outlined.

The first is to maximise recruitment, especially in centres that are currently under-recruiting. This will be achieved using the new network of Gynaecological Cancer Leads in the fifteen Clinical Research Network regions as local champions. This strategy will also require that clinical trials be opened in as many centres as possible, rather than only in centres that have traditionally recruited. Innovative trial designs, such as umbrella studies, will reduce downtime between trials, thereby improving overall recruitment.

The second is to broaden the portfolio. In particular this will involve collaboration with other CSG in the areas of prevention (most pressingly in obesity-induced endometrial cancer), survivorship and supportive and palliative care.

Finally, through the NCRI and ECMC networks, the CSG has a unique opportunity to lead stratified, biomarker-driven trials in gynaecological cancers, with associated translational research. TR-ICON7 and TR-ICON8 have ensured that multiple biological specimens (for example tumour, germline DNA, circulating tumour DNA) have been collected, which will facilitate multiple translational research projects.

Already, plans are being developed for a biomarker-drive trial in first-line high grade serous ovarian cancer. Imaginative partnership with industry as well as international collaboration will be required to ensure the success of such studies.

Ovarian Subgroup (Chair, Dr Ros Glasspool)

The Subgroup had two meetings this year, one in September in London and a joint meeting with the Scottish Gynaecological Cancer Trials Group in February in Glasgow. Both meetings were, once again, very well attended. The main meetings allow investigators to present new concepts to the subgroup for comments and advice. They provide an update to investigators around the

country on current trials and those in development, and a forum for discussion. Key successes of the group include the completion ICON8 ahead of time, with 1566 patients recruited from 97 UK centres with the majority also consenting to the parallel translational study, TR-ICON 8. ICON8B is due to open later in 2015. The UK was also the joint highest recruiter to the Symptom Benefit study, an international study led by ANZGOG.

The Subgroup has been successful in seeking funding or endorsement from CTAAC for several studies including OCTOPUS (weekly paclitaxel +/- AZ2014) in platinum resistant recurrent disease. This is the first arm of a planned rolling phase II design that will investigate novel paclitaxel combinations. With the aim of developing a pipeline of potential combinations, NAC funding was also secured through the ECMC Combinations Alliance for a phase I study of the Hedgehog inhibitor LY2940680 with weekly paclitaxel.

Improving outcomes for rare ovarian tumours is a priority area for the Subgroup. The NiCCC study, a UK led international study in relapsed clear cell carcinoma opened in April 2015 and the LOGS study in low grade serous tumours will open imminently.

One of the aims of the Subgroup is to improve access to trials for women across the country. To support this, a list of investigators interested in future studies has been generated and is being offered to those looking to run both industry and academic studies. This will facilitate inclusion of centres that might otherwise not have been approached.

Endometrium Subgroup (Chair, Professor Richard Edmondson)

A successful subgroup workshop was held on 24th April 2015 in conjunction with the cervix subgroup. The meeting was attended by 36 people from a wide range of disciplines including surgical and non surgical oncology, pathology and nursing. A further joint workshop with the cervix subgroup will be held next year. The Endometrium Subgroup has also supported the work of the Womb Cancer Alliance. Working with the James Lind Alliance, this initiative aims to identify research priorities using an established survey technique, which will inform the future research agenda.

The funding of the STATEC trial by CTAAC was a major boost. This will be a flagship trial, led by the UK. The added benefit of a sentinel node sub-study will allow centres to gain experience of this important technique. The portfolio now also includes several prevention studies in high risk population. The Endometrium Subgroup will use this experience from these single-centre trials to develop future multi-centre prevention studies.

PARAGON, the phase II study of aromatase inhibitor therapy in hormone receptor positive tumours, has now completed recruitment of the endometrial cancer arm but is still open to recruitment for uterine sarcomas. Results are expected in the third quarter of 2015 for the endometrial arm and a successor study will be planned thereafter.

ENDCAT completed recruitment and preliminary results confirm that telephone follow up is an acceptable and cost effective strategy for the follow up of low grade, low stage endometrial cancer patients. A manuscript is currently in preparation and the Subgroup supports the development of further implementation studies.

The CSG plays a major role in translational studies related to PORTEC3 (the transPORTEC collaboration) and work continues on trans-PARAGON (first results due mid 2016)

Finally, the Subgroup supports trials in rare tumours, including gynaecological sarcomas and gestational trophoblastic disease.

Cervix/Vulva Subgroup (Chair, Professor Nick Reed)

The Cervix Subgroup consists of a core of ten individuals, but with a wider network of around twenty-five clinical and medical oncologists, pathologists, radiologists and surgeons around the UK. Highlights of the past 12 months include the presentation, at ESMO 2014, of the CIRCCa study. This showed a small survival advantage to the addition of cediranib in patients with relapsed cervix cancer receiving carboplatin and paclitaxel chemotherapy. In addition, the SHAPE study, which investigates whether less radical surgery (simple hysterectomy with lymphadenectomy) is a safe option compared to radical hysterectomy for localised cervical cancer, was launched in the UK on 24th April 2015.

The principal study at present is INTERLACE, which investigates neo-adjuvant chemotherapy in locally advanced cervix cancer. Although recruitment has been poor, it is hoped that this will now start to pick up as most large UK gynaecological cancers are now open to recruitment. The Subgroup is awaiting the opening of ENGOT CX02 for relapsed disease and discussions are on-going regarding a successor to CIRCCa.

Several other studies continue to recruit, including MAPPING, EPIVIN, DEPICT and GROINSS-V2. Further initiatives are being developed involving novel agents for patients receiving third line treatment. These include weekly paclitaxel and new investigational agents, the use of PDL1 Inhibitors and immunotherapy approaches. Further initiatives include treatment for locally advanced, un-resectable vulval cancer, recurrent vulval cancer, and a portfolio of studies in HPV-associated cancers of the vulva, anus and cervix in collaboration with the Colorectal CSG. Finally, biomarker studies in vulval cancer and VIN3are being developed as well as studies for treatment of Lichen Sclerosis-associated vulval cancer.

4. Task groups/Working parties

As in 2013 – 14, it is acknowledged that rare cancers pose a specific challenge in gynaecological cancers. Through collaboration with the British Association of Gynaecological Pathologists, a group is developing a national strategy in this area, to ensure consistent pathological detection and accurate clinical data collection.

5. Patient recruitment summary for last 5 years

Recruitment to Gynae CSG trials continues to be adequate. The percentage of patients entering interventional trials has been consistently around 4 – 5% over the past 3 years. As previously, single very large trials dominate recruitment – ICON8 recruited a total of 1566 patients, with an average of 55 patients per month in its last year. Thus, it is possible for gynaecological cancer trials to recruit rapidly. It will be important that the overall portfolio continues to have major studies that can be run in all centres. In 2015 – 16, these major trials will be ICON8B (ovarian cancer), INTERLACE (cervix cancer) and STATEC (endometrial cancer). It is vital that these trials recruit rapidly in as many centres as possible.

There remain two clear features of recruitment. The first is that ovarian cancer currently dominates. In 2013 – 14, over half of recruitment (55%: 1375/2451) into trials of patients with known cancer involved ovarian cancer. There have been large endometrial cancer trials (PORTEC3, ASTEC) previously, demonstrating that broad recruitment need not be limited to

ovarian cancer studies. However, recruitment to INTERLACE is currently behind schedule and urgent action is being taken to improve this – INTERLACE has highlighted the challenges of running gynaecological cancer trials in which radiotherapy is a key component: ensuring Quality Control and consistent planning, especially of Intensity Modulated Radiotherapy (IMRT), have been challenging.

The second clear feature is geographical variation in recruitment. The charity Target Ovarian Cancer has undertaken a major piece of work in ovarian cancer, mapping regional differences in recruitment – the data are illuminating, with an eight-fold difference between the top and bottom quartiles of recruitment by CRN. The CSG will work with the fifteen new gynaecological leads from the fifteen Clinical Research Networks – the role of the CRN leads will be to champion gynaecological cancer trials and identify suitable investigators to run trials.

In the Gynae CSG portfolio, 20 trials closed to recruitment and 19 opened.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2010/2011	1885	357	1441	357	9.4	2.3
2011/2012	4763	597	4389	597	28.6	3.9

Table 2 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	335	10750	183	754	1.0	4.3
2013/2014	1809	823	1628	823	9.3	4.7
2014/2015	899	891	705	869	4.0	5.0

6. Links to other CSGs, international groups and network subspecialty leads

Given the relative rarity of each individual gynaecological cancer type, international collaboration is essential and the Gynae CSG has a prominent international outlook. Members of the CSG continue to represent the Group at the GCIG (Gynecologic Cancer InterGroup) meetings and at ENGOT (European Network for Gynaecological Oncology Trials). These groups both meet twice a year. The CSG has 4 members and the MRC sends two members to these meetings. Professor Jonathan Ledermann is co-chair of the Rare Tumour Subgroup at GCIG, whilst Professor McNeish is chair of the translational committee of ENGOT. In addition, the CSG sent two members (Dr Andrew Clamp and Dr Shibani Nicum) to the ENGOT Gynaecological Cancer Academy from 2013 - 15. This new group seeks to develop the next generation of leaders in Gynaecological Cancer in Europe, and meets three times per year with workshops and networking events. Two new representatives, Dr Susana Banerjee and Dr Alex Taylor, will represent the CSG in 2015 – 2017.

The CSG will also be well represented at the 5th Ovarian Cancer Consensus Conference in Toyko in November 2015. Members of the CSG self-fund travel to these meetings and the MRC pays the annual subscription to the GCIG.

Links to other CSG are more embryonic – however, representatives from the CSG will attend inaugural clinical trials planning meeting of the Supportive & Palliative Care CSG in June 2015. Collaboration with the Primary Care CSG will be developed for prevention studies in endometrial cancer in particular.

The importance of the CRN network gynaecological cancer leads is described above – these appointments are new and the role will certainly evolve over the next 12 - 18 months. Regular contact with these leads will also be important to maintain momentum.

The NCRI Gynae CSG has taken the initiative to strengthen the relationship between the trials/research component of the CSG and the BGCS, the main professional body representing gynaecological oncology. BGCS is a predominately a surgical organisation, originating from within the Royal College of Obstetrics and Gynaecology. Through joint meetings and broader membership, we are beginning to see an increasing number of surgical trial ideas emerge. A second joint meeting of the NCRI Gynae CSG and BGCS took place in July 2014 and a new, non-surgical, subgroup of the BGCS is being established with CSG leadership.

7. Funding applications in last year

The CSG has had continued success with competitive funding in 2014 – 15. Most applications are sent to Cancer Research UK CTAAC either for funding or endorsement. However, there has also been success with NIHR: Professor Andrea Rockall led a bid to the NIHR Health Technology Assessment to investigate the role of multi-parametric MRI in the diagnosis and decision making in advanced ovarian cancer. This study will commence set-up in December 2015.

A novel funding source emerged in 2015 – NICE (National Institute for Heath and Care Excellence) commissioned research to inform revision of guidance in 2018 on surgery in ovarian cancer. Emerging from this commission, SOCQER-2 (Surgery in Ovarian Cancer – Quality of Life, Efficacy Research) will evaluate prospectively short term and long term patient-reported outcome measures in women undergoing extensive debulking surgery for advanced stage ovarian cancer compared to those undergoing standard surgery. It will also evaluate 18 month and 24 month survival in both groups. This is the first time that NICE has commissioned a specific study in gynaecological cancer ahead of guideline revision.

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
OCTOPUS (TAX-TORC2): A randomised phase II trial of AZD2014 and paclitaxel in platinum-resistant ovarian cancer	Feasibility application	Dr Susana Banerjee	Endorsed
PETROC: A phase II/III study of intraperitoneal (IP) plus intravenous (IV) chemotherapy versus IV carboplatin plus paclitaxel in patients with epithelial ovarian cancer optimally debulked at	Full application	Dr Chris Gallagher	Funded

surgery following neoadjuvant intravenous chemotherapy			
STATEC: A randomised trial of non-selective versus selective adjuvant therapy in high risk endometrial cancer	Full application	Mr Tim Mould and Professor Henry Kitchener	Not funded
ROSIP: A feasibility study on the role of surgery in peritoneal cancer	Feasibility application *Resubmission*	Professors Sean Kehoe and Richard Clayton	Not funded
November 2014			
PORTEC-4: Postoperative Radiation Therapy for Endometrial Carcinoma Multicentre Randomised Phase III Trial Comparing Vaginal Brachytherapy (Two Dose Schedules) with Observation after Surgery	Full Application	Dr Melanie Powell	Achieved fundable score – endorsement offered
Single arm feasibility study of Cediranib plus standard chemotherapy and IMRT for stage III/IV HPV induced squamous carcinomas in cervix, anus and vulva	Feasibility Application	Dr Marcia Hall	Not funded
INOVATYON - Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with relapsed ovarian cancer progressing within 6-12 months of last platinum	Outline Application	Dr Ana Montes	Full application invited
STATEC: A randomised trial of non-selective versus selective adjuvant therapy in high risk endometrial cancer	Full application (re-application)	Mr Tim Mould and Professor Henry Kitchener	Funded
March 2015			
ICON9: An international phase 3 randomised trial of cediranib and olaparib maintenance in patients with relapsed platinum sensitive ovarian cancer	Outline application	Dr Shibani Nicum	Full application invited
Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with relapsed ovarian cancer progressing within 6-12 months of last platinum	Full application	Dr Ana Montes	Funded
Randomised Trial of Olaparib vs weekly Taxol vs Cediranib and Olaparib in Patients with Relapsed Platinum Resistant BRCA Mutated Ovarian Cancer	Feasibility application *Endorsement*	Dr Shibani Nicum	Endorsed
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Impact of multiparametric MRI on staging and management decisions in women with ovarian cancer. (MROC – MRI in Ovarian Cancer)	NIHR Health Technology Assessment (outline and then full)	Professor Andrea Rockall	Funded (Nov 2014)
SOCQER-2 - Surgery in Ovarian Cancer – Quality of Life, Efficacy Research	NICE - commissioned	Dr Sudha Sundar	Funded

8. Collaborative partnership studies with industry

The CSG has a history of a successful collaboration with industry partners such as Roche, AstraZeneca, GSK and Boehringer Ingelheim, who have all supported academic trials in gynaecological cancer. The models of support have varied and include CTAAC or ECMC Alliance (NAC) funding, full industry support for investigator-initiated trials or hybrid funding. These arrangements are complex and rely greatly of the negotiations between the Clinical Trials Unit developing the trial, Industry and the Chief Investigator. Encouragingly, new proposals in collaboration with AZ and Eli Lilly have been developed by and with the CSG during 2014 – 15. These include TAX-TORC2, a randomised phase II trial of AZD2014 and paclitaxel in platinum-resistant ovarian cancer. This will be the first arm of OCTOPUS (Ovarian Cancer Trials of Paclitaxel – Umbrella Study), which will be a rolling trial for women with platinum-resistant ovarian cancer with weekly paclitaxel as the control arm, to which arms containing novel agents can be added, either as single agent or in combination with the paclitaxel. Weekly paclitaxel is the agreed first-choice regime for women with platinum-resistant ovarian cancer, and the SaPPrOC study demonstrated that there is enthusiasm for recruiting into trials with this as control arm.

The number of commercial studies on the portfolio continues to rise, both in absolute numbers and proportion of the overall portfolio. The CSG is enthusiastic about collaboration with industry – however, there needs to be vigilance to ensure that commercial studies are not adopted onto the portfolio where there is a direct clash with academic studies and also to encourage industry to open studies beyond a narrow range of sites. The CSG, in particular the ovary subgroup, has developed lists of new centres, with experience in large studies such as ICON8, that are keen to participate in industry studies.

9. Impact of CSG activities

The Group has led several practice changing trials over the last 5 years, with an excellent record of presentation at international meetings and publication in high-impact journals. The key results are:

OV05, a CA125 follow up study, showed there is no advantage to early implementation of second-line chemotherapy for recurrent ovarian cancer. Whilst questioning the value of CA125 follow up, it has given clinicians the re-assurance that patients with rising CA125 who are well do not need early chemotherapy. As a result they have a prolongation of a good quality of life.

The UK-led ICON 7 trial of bevacizumab in front-line treatment of ovarian cancer was key in assisting clinicians with decision-making about selecting the most appropriate patients for therapy. This was not evident in the data submitted for licensing. Also, the dose used was 50% of the licensed dose. However, this dose and the identification of the group most likely to benefit from the drug have been instrumental in guiding the Cancer Drug Fund process for approval. NICE has not give approval for the use of bevacizumab in first-line treatment of ovarian cancer however.

The Group contributed to EORTC 55971, a trial comparing primary (neoadjuvant) chemotherapy with primary surgery followed by chemotherapy, and led a subsequent trial, CHORUS, with a very similar design. The EORTC trial has led to a significant change in practice, confirming the absence of detriment in survival by delaying surgery in a group of women who present with

advanced disease. CHORUS has shown similar results (ASCO 2013 – publication pending) and as a result UK, European and to some extent US practice has changed. A greater proportion of patients now have primary chemotherapy. CHORUS has also shown that postoperative hospital stay is reduced in those undergoing delayed surgery.

The CSG also contributed to critical studies of the PARP inhibitor olaparib. Critical to this was Study 19, which showed that maintenance olaparib following response to platinum-based chemotherapy in relapsed ovarian cancer, led to dramatic increases in progression-free survival, especially in those patients with germline or somatic mutations in *BRCA1* or *BRCA2*. These data led to the European licensing of olaparib in 2015.

10. Consumer involvement

Our consumers offer regular valued input to the CSG, providing insight from the patient perspective, both at the main CSG meetings and at subgroups. In addition they are involved in a number of CSG studies, at various stages from application to TMG. They have both undertaken training this year to improve their ability to contribute to studies.

Detailed consumer review through the CSG was given to both CTAAC and Population Research Committee applications.

Mrs Hilary Stobart is a TMG member of the INTERLACE study, looking at locally- advanced cervical cancer, and a co-applicant and now study team member for the RocKETS study (risk models in ovarian cancer diagnosis). In addition she is a member of CTRad and is involved in VOXTOX and REQUITE, both studying radiation toxicity, including in the pelvis. She was a co-author of 'Comfort Blanket or Clinical Need? The Role of Follow-up for Cancer Survivors', a Clinical Oncology (2014) editorial, and presented at Britain against Cancer (December 2014) in a joint CR-UK/NCIN/ICPV session 'It's our Data'.

Mrs Angela Stagg joined the CSG in June 2014. Since starting she has provided comment on research bids, including for CTAAC, and patient leaflets. She has also joined as a member of the CSG endometrial sub-group. In her local area, she has been involved in 'People in Health West of England' an umbrella organisation across the local CLAHRC, AHSN and other networking groups involved in linking up service provision and research. She has been on working groups e.g. project evaluation, and been the consumer member on interview panels for project staff.

11. Open meetings/annual trials days/strategy days

There has not been a trials meeting since December 2013. However, following on from the success of the 2013 meeting, a second Gynae CSG trials meeting will take place in December 2015 at the Royal College of Physicians in London.

A CSG strategy meeting took place in Glasgow in February 2015 – attended by the CSG chair, subgroup chairs and two other attendees. The purpose of the meeting was to devise a broad direction for the CSG over the next five years. Details are given in Appendix 2.

Disappointingly, a planned CSG Roadshow to the South Coast (Kent and Sussex) to be held in Worthing in March 2014 was cancelled due to poor registration.

12. Progress towards achieving the CSG's 3 year strategy

The first CSG strategy meeting was only held on 24th February 2015, at which key aims and priorities were set for the coming three years (see Appendix 2). However, steps towards achieving those aims and priorities have already been taken:

- Core trials role. New trial ideas being developed in platinum-sensitive relapsed ovarian cancer, clear cell carcinoma of the ovary, risk reduction in patients with germline *BRCA* mutations, as well as relapsed endometrial cancer.
- Recruitment. The CSG chair and ovary subgroup chair met with some of the new CRN Gynae Oncology leads on 9th March to develop methods for improving recruitment in their regions.
- Next generation. Two new representatives from the CSG have been chosen to participate in the ENGOT Gynaecological Cancer Academy for 2015 – 2017

13. Priorities and challenges for the forthcoming year

The three key priorities and challenges for 2015 – 2016 are as follows:

Priorities: recruitment, inclusion, expansion

Challenges: recruitment, efficiency, impact

Recruitment (both a priority and a challenge). It is self-evident that our studies must recruit both to time and to target. ICON8 recruited extremely well, INTERLACE is doing less well. ICON8B and STATEC must succeed. For our smaller studies, especially those in specific subtypes of ovarian cancer, monitoring recruitment will be particularly important. It will also be important to increase recruitment in those areas of the country where there is little participation in clinical studies. The appointment of local Gynae Cancer leads is critical, especially their ability to enthuse and motivate.

Inclusion and expansion (priorities). There is a need to ensure that clinical trials open in as many centres as possible. There is clear evidence that patients are willing to travel in order to participate in clinical trials – oncologists must be prepared to refer patients to centres that are running specific trials (e.g. for specific rarer subtypes) if not open in their centre. The work by Target Ovarian Cancer reveals great variation across the country that must be addressed. Similarly, the CSG will work to open studies as widely as possible and also to ensure that the portfolio still includes large phase III studies that can be opened universally.

'Inclusion' and 'expansion' also mean that the portfolio needs to include trials for patients at all points in their cancer treatment. This will include supportive and palliative care and also prevention studies. Thus, the priority is to extend the scope of the portfolio beyond the CSG's standard areas, with co-operation and collaboration with other CSGs.

Efficiency (challenge). Recruitment is the most obvious target for any clinical trial. However, time to trial opening following funding, completeness of data collection and speedy publication of primary trial outcome data are all vitally important in ensuring the success of trials. This is particularly challenging for international trials

Impact (challenge). Running clinical trials is the core activity of the CSG. However, it is clear that completion of a clinical trial and publication of results is only a first step to improving patient care. Results of clinical trials need to translate into routine clinical practice – the CSG has a key

role in providing expert leadership to help shape treatment guidelines. In addition, CSG expertise is essential in the various national approval processes (including NICE, Cancer Drugs Fund and the Scottish Medicines Consortium), which ensure maximum long-term impact from our clinical trials.

14. Concluding remarks

The NCRI Gynaecological Cancer Clinical Studies Group is a scientifically influential international organisation that runs a broad and diverse portfolio of clinical trials in the three main gynaecological cancers. The Group continues to deliver practice-changing clinical research in its traditional areas of strength, especially ovarian cancer, but must now expand into newer areas, especially in the arenas of prevention and early diagnosis, as well as in vulval cancer.

Key priorities for the group in the coming years also include ensuring that there is consistent recruitment around the whole of the UK as well as equitable access to clinical trials for patients in all parts of the country. Trials need to open rapidly, recruit to target and report outcomes speedily

Translational research has been embedded into our clinical trials in ovarian cancer for several years; it is highly encouraging that this is now expanding into studies in cervix and endometrial cancers.

Finally, the CSG has had definite impact in the treatment of gynaecological cancers in the UK and internationally and we must continue to run clinical studies that will not only shape clinical practice but address fundamental questions of cancer biology for years to come.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Appendix 6 – Strengths & Weaknesses from the Gynae CSG 2014 Progress Review

Professor Iain McNeish (Gynae CSG Chair)

Appendix 1

Membership of the Gynae CSG

Name	Specialism	Location
Dr Debra Josephs*	Medical Oncologist	London
Dr Emma Crosbie	Gynaecological Oncologist	Manchester
Professor Richard Edmondson	Gynaecological Oncologist	Manchester
Dr Christina Fotopoulou	Gynaecological Oncologist	London
Ms Emma Hudson	Clinical Oncologist	Cardiff
Dr Melanie Powell	Clinical Oncologist	London
Professor Nicholas Reed	Clinical Oncologist	Glasgow
Dr Alexandra Taylor	Clinical Oncologist	London
Dr Michelle MacKintosh*	Gynaecological Oncologist	Manchester
Mrs Angela Stagg (CLG)	Consumer	Bristol
Mrs Hilary Stobart (CLG)	Consumer	Nottingham
Dr Susana Banerjee	Medical Oncologist	London
Dr Andrew Clamp	Medical Oncologist	Manchester
Dr Ros Glasspool	Medical Oncologist	Glasgow
Dr Marcia Hall	Medical Oncologist	Middlesex
Professor Jonathan Ledermann	Medical Oncologist	London
Dr Michelle Lockley	Medical Oncologist	London
Dr Rosemary Lord	Medical Oncologist	Merseyside
Professor Iain McNeish (Chair)	Medical Oncologist	Glasgow
Dr Agnieszka Michael	Medical Oncologist	Guildford
Dr Shibani Nicum	Medical Oncologist	Oxford
Dr Lynn Hirschowitz	Pathologist	Birmingham
Mr Jim Paul	Statistician	Glasgow

* denotes trainee

Membership of the Subgroups

Ovarian Subgroup		
Name	**Specialism**	**Location**
Mrs Hilary Stobart	Consumer	Nottingham
Mrs Sundha Sundar	Gynaecological Oncologist	Birmingham
Dr Ros Glasspool (Chair)	Medical Oncologist	Glasgow
Dr Susie Banerjee	Medical Oncologist	London
Professor Jonathan Ledermann	Medical Oncologist	London
Dr Rosemary Lord	Medical Oncologist	Merseyside
Professor Iain McNeish	Medical Oncologist	Glasgow
Dr Shibani Nicum	Medical Oncologist	Oxford
Dr Sarah Williams	Medical Oncologist	Birmingham
Dr Nafisa Wilkinson	Pathologist	Leeds

Endometrial Subgroup		
Name	**Specialism**	**Location**
Dr Jane Orton	Clinical Oncologist	Leeds
Dr Melanie Powell	Clinical Oncologist	London
Dr Nick Reed	Clinical Oncologist	Glasgow
Dr Alex Taylor	Clinical Oncologist	London
Dr Emma Crosbie	Gynaecological Oncologist	Manchester
Professor Richard Edmondson (Chair)	Gynaecological Oncologist	Manchester
Dr Andrew Clamp	Medical Oncologist	Manchester
Dr Rebecca Kristeleit	Medical Oncologist	London
Professor Jonathan Ledermann	Medical Oncologist	London
Dr Axel Walther	Medical Oncologist	Bristol

Cervix/Vulva Subgroup		
Name	**Specialism**	**Location**
Dr Peter Baldwin	Clinical Oncologist	Cambridge
Dr Susan Davidson	Clinical Oncologist	Manchester
Dr Mary McCormack	Clinical Oncologist	London
Dr Melanie Powell	Clinical Oncologist	London
Professor Nick Reed (Chair)	Clinical Oncologist	Glasgow
Dr Paul Symonds	Clinical Oncologist	Leicester
Mr Raj Naik	Gynaecological Oncologist	Gateshead
Dr Laurence Brown	Histopathologist	Leicester
Dr Lynn Hirschowitz	Pathologist	Birmingham
Dr Andrea Rockall	Radiologist	London
Dr Isabella White		London

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The CSG strategy meeting on 24th February 2015 highlighted nine key points that will be used to direct the group over the next 3 years.

1. The CSG core strategy remains to develop, lead and participate in innovative clinical trials that address key questions in gynaecological cancer and that have the potential to change routine clinical practice both in the UK and the rest of the world.
2. The CSG will aim to increase diversity of membership, in particular to seek applications from radiologist and Clinical Nurse Specialists, to complement to current membership that represents surgery, clinical and medical oncology, and pathology.
3. The CSG will ensure that approval mechanisms are clearer, with more formal pathway for subgroup approval.
4. The CSG will continue to develop the next generation of leaders in Gynae cancer, starting with a new Cervical Subgroup Chair in 2015, new attendees at the ENGOT Gynae Cancer Academy and encouraging trainee members on the CSG.
5. The CSG will increase the role of consumers within the CSG by ensuring active mentoring, greater education and earlier involvement in trials development
6. Through closer working with the new Clinical Research Network structures, the CSG aims to improve trial recruitment, especially in low-recruiting networks.
7. Th CSG will ensure that appropriate translational sample collection is completely integral to trial protocol from first draft.
8. In addition to applications to CTAAC, the CSG will aim to diversify sources of funding for clinical trials, with increased applications to NIHR and MRC funding schemes.
9. The CSG aims to improve working with other CSGs – key priorities include a new study of primary prevention of endometrial cancer in conjunction with primary care CSG, and a study of targeted therapy in HPV-positive ano-genital cancers in assocation with the colorectal CSG.

In addition to the over-arching strategies of the whole CSG, the three subgroups have their own key and specific strategic aims for the next 3 years.

B – Ovarian Subgroup Strategy

1. To develop a new trial of first line chemotherapy in elderly patients.
2. To develop a first-line biomarker-driven study in high grade serous ovarian cancer.

C – Endometrial Subgroup Strategy

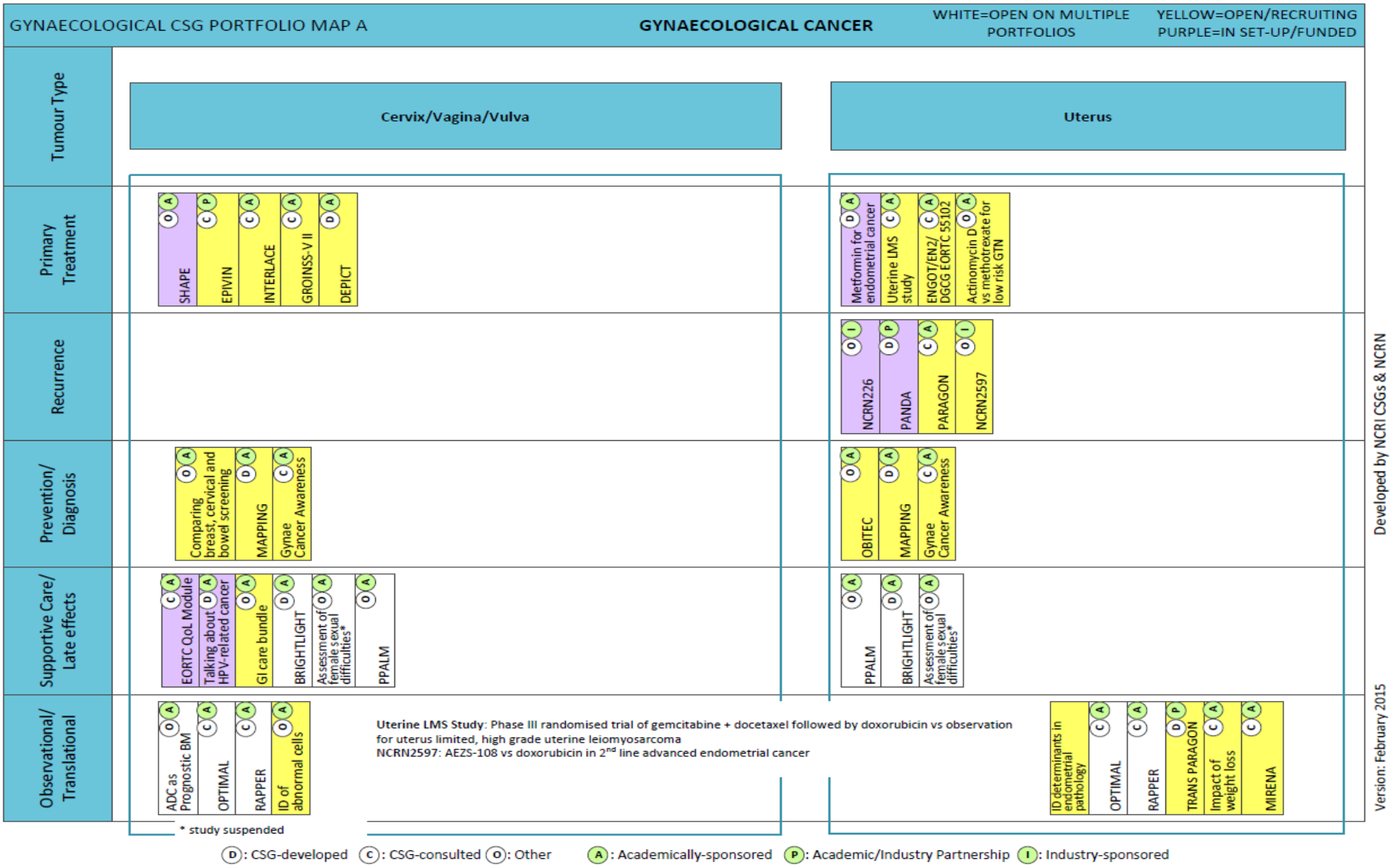
1. To develop new trials of primary prevention in high risk patients, in conjunction with primary care CSG
2. To develop a new biomarker-driven study in high-risk first line patients and/or relapsed disease.

D – Cervix/Vulva Strategy

1. To develop a new trial in relapsed disease to follow on from CIRCCA
2. To develop a trial directed specifically at HPV-positive ano-genital malignancies in conjuction with the colorectal MDT
3. To develop one new therapy trial in relapsed vulva cancer with associated tissue collection

Appendix 3

Portfolio maps



GYNAECOLOGICAL CSG PORTFOLIO MAP B

GYNAECOLOGICAL CANCER

WHITE=OPEN ON MULTIPLE PORTFOLIOS

YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED

Tumour Type	Primary Treatment	Recurrence	Prevention/ Diagnosis	Supportive Care/ Late effects	Observational/ Translational
Ovary/Fallopian Tube	PETROC/OV21 (D, A) ICON8* (D, A) Ovarian Tumour DNA Methylation (C, A) NCRN2371/ SOLO1 (O, I)	NCRN378b (O, I) NCRN 2352/ PISARRO (O, I) NCRN 2789 (D, P) NCRN 2746/ ARIEL3 (O, I) NCRN 2434/ ARIEL2* (C, I) CORAL (C, P) TRIOC (D, P) NCRN509/OSCAR 1 (C, I) ProGem2 (C, I) NCRN 2489 (O, I) INOVATYON * (O, P) PARAGON (D, P) PAZ-PET (O, I) DESKTOP III (C, A) NiCCC Trial (D, P) METRO-BIBF (D, P) PAZOFOS (D, P) NCRN 2643 (O, I) AGO-OVAR 2.21/ENGOT-ov18 (D, A) NCRN396/ VE BASKET (O, I)	ROCkeTS (D, A) ICBP module 4 (O, A) EMBRACE (C, A) CRUK Stratified Medicine (C, P) Gynae Cancer Awareness (C, A) DNA Methylation Study (C, A)	PPALM (O, A) BRIGHTLIGHT (D, A) OvPSYCH 2 (D, A)	ICON3 p53 TRICON8: GI symptoms in OC (O, A) Ovarian Tumour DNA methylation (C, A) GTEOC (O, A) Microfluidic device for pro coagulant changes (O, A) DISCOVAR (C, A) Ovarian tumour genetics & patient outcome (O, A) BriTROC1 (D, A) Ovarian tissue culturing (O, A) Phase I study of AT13148 (O, A) CTCR-OV04 (O, A) AVALPROFS

NCRN396: Open label, phase II of vemurafenib in BRAF V600 mutation-positive cancers
NCRN509/OSCAR 1: Observational study of Avastin as first-line therapy in advanced ovarian ca
NCRN – 2371: 1st line olaparib maintenance therapy in BRCA ovarian cancer
NCRN – 2434/ ARIEL2: Rucaparib in Pt-sensitive relapsed, high grade gynaecological cancer
NCRN – 2489: A Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer
NCRN – 2643: DNIB0600A in patients with Pt-resistant ovarian cancer
NCRN – 2746/ ARIEL3: Rucaparib in Pt-sensitive high grade gynae cancer

* study suspended

(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

Developed by NCRI CSGs & NCRN

Version: February 2015

Appendix 4

Publications in the reporting year

ICON7

Backen A, Renehan AG, Clamp AR, Berzuini C, Zhou C, Oza A, Bannoo S, Scherer SJ, Banks RE, Dive C, Jayson GC. The combination of circulating Ang1 and Tie2 levels predicts progression-free survival advantage in bevacizumab-treated patients with ovarian cancer (ICON7). *Clin Cancer Res* 2014;20(17):4549-58.

Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Park-Simon TW, Rustin G, Joly F, Mirza MR, Plante M, Quinn M, Poveda A, Jayson GC, Stark D, Swart AM, Farrelly L, Kaplan R, Parmar MK, Perren TJ. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015.

OVATURE

Fotopoulou, C., I. Vergote, P. Mainwaring, M. Bidzinski, J. B. Vermorken, S. A. Ghamande, P. Harnett, S. A. Del Prete, J. A. Green, M. Spaczynski, S. Blagden, M. Gore, J. Ledermann, S. Kaye and H. Gabra (2014). Weekly AUC2 carboplatin in acquired platinum-resistant ovarian cancer with or without oral phenoxodiol, a sensitizer of platinum cytotoxicity: the phase III OVATURE multicenter randomized study. *Ann Oncol* 25(1): 160-165.

MK0143

Rockall AG, Avril N, Lam R, Iannone R, Mozley PD, Parkinson C, Bergstrom DA, Sala E, Sarker SJ, McNeish IA, Brenton JD, (2014), Repeatability of quantitative FDG-PET/CT and contrast enhanced CT in recurrent ovarian carcinoma: test retest measurements for tumor FDG uptake, diameter and volume (MK-0143), *Clin Cancer Res*. 2014;20(10):2751-60

CA125 Doubling

Hall MR, Petruckevitch A, Pascoe J, Persic M, Tahir S, Morgan JS, Gourley C, Stuart N, Crawford SM, Kornbrot DE, Qian W, Rustin GJ. Using serum CA125 to assess the activity of potential cytostatic agents in ovarian cancer (CA125 doubling). Int J Gynecol Cancer 2014;24(4):676-81.

6MP/MTX study

Nicum S, Roberts C, Boyle L, Kopijasz S, Gourley C, Hall M, Montes A, Poole C, Collins L, Schuh A, Dutton SJ. A phase II clinical trial of 6-mercaptopurine (6MP) and methotrexate in patients with BRCA defective tumours: a study protocol (6MP/MTX). BMC Cancer 2014;14:983.

SaPPrOC

McNeish IA, Ledermann JA, Webber L, James L, Kaye SB, Hall M, Hall G, Clamp A, Earl H, Banerjee S, Kristeleit R, Raja F, Feeney A, Lawrence C, Dawson-Athey L, Persic M, Khan I. A randomised placebo-controlled trial of weekly paclitaxel and saracatinib (AZD0530) in platinum-resistant ovarian, fallopian tube or primary peritoneal cancer (SaPPrOC). Ann Oncol 2014;25(10):1988-95.

DACROC

Glasspool RM, Brown R, Gore ME, Rustin GJ, McNeish IA, Wilson RH, Pledge S, Paul J, Mackean M, Hall GD, Gabra H, Halford SE, Walker J, Appleton K, Ullah R, Kaye S. A randomised, phase II trial of the DNA-hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in combination with carboplatin vs carboplatin alone in patients with recurrent, partially platinum-sensitive ovarian cancer (DACROC). Br J Cancer 2014;110(8):1923-9.

Guideline publications from Gynecologic Cancer InterGroup with CSG authorship

Satoh T, Takei Y, Treilleux I, Devouassoux-Shisheboran M, Ledermann J, Viswanathan AN, Mahner S, Provencher DM, Mileshkin L, Avall-Lundqvist E, Pautier P, Reed NS, Fujiwara K. Gynecologic Cancer InterGroup (GCIG) consensus review for small cell carcinoma of the cervix. Int J Gynecol Cancer 2014;24(9 Suppl 3):S102-8.

Ledermann JA, Luvero D, Shafer A, O'Connor D, Mangili G, Friedlander M, Pfisterer J, Mirza MR, Kim JW, Alexandre J, Oza A, Brown J. Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma. Int J Gynecol Cancer 2014;24(9 Suppl 3):S14-9.

Ray-Coquard I, Brown J, Harter P, Provencher DM, Fong PC, Maenpaa J, Ledermann JA, Emons G, Rigaud DB, Glasspool RM, Mezzanzanica D, Colombo N. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian sex cord stromal tumors. Int J Gynecol Cancer 2014;24(9 Suppl 3):S42-7.

Harter P, Gershenson D, Lhomme C, Lecuru F, Ledermann J, Provencher DM, Mezzanzanica D, Quinn M, Maenpaa J, Kim JW, Mahner S, Hilpert F, Baumann K, Pfisterer J, du Bois A. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian tumors of low malignant potential (borderline ovarian tumors). Int J Gynecol Cancer 2014;24(9 Suppl 3):S5-8.

Berton-Rigaud D, Devouassoux-Shisheboran M, Ledermann JA, Leitao MM, Powell MA, Poveda A, Beale P, Glasspool RM, Creutzberg CL, Harter P, Kim JW, Reed NS, Ray-Coquard I. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. Int J Gynecol Cancer 2014;24(9 Suppl 3):S55-60.

Glasspool RM, Gonzalez Martin A, Millan D, Lorusso D, Avall-Lundqvist E, Hurteau JA, Davis A, Hilpert F, Kim JW, Alexandre J, Ledermann JA. Gynecologic Cancer InterGroup (GCIG) consensus review for squamous cell carcinoma of the ovary. Int J Gynecol Cancer 2014;24(9 Suppl 3):S26-9.

Okamoto A, Glasspool RM, Mabuchi S, Matsumura N, Nomura H, Itamochi H, Takano M, Takano T, Susumu N, Aoki D, Konishi I, Covens A, Ledermann J, Mezzazanica D, Steer C, Millan D, McNeish IA, Pfisterer J, Kang S, Gladieff L, Bryce J, Oza A. Gynecologic Cancer InterGroup (GCIG) Consensus Review for Clear Cell Carcinoma of the Ovary. Int J Gynecol Cancer 2014;24(9 Suppl 3):S20-s25.

Appendix 5

Major international presentations in the reporting year

ICON7

Charlie Gourley, Andrena McCavigan, Timothy Perren, James Paul, Caroline Ogilvie Michie, Michael Churchman, Alistair Williams, W. Glenn McCluggage, Mahesh Parmar, Richard S. Kaplan, Laura A. Hill, Iris A Halfpenny, Eamonn J. O'Brien, Olaide Raji, Steve Deharo, Timothy Davison, Patrick Johnston, Katherine E. Keating, D. Paul Harkin, Richard D. Kennedy. Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab. J Clin Oncol 32:5s, 2014, ASCO 2014

Appendix 6

Strengths & weaknesses from the 2014 Progress Review

Strengths:

- The strong leadership shown by Professor Ledermann and the previous Chair Professor Kitchener
- The successful completion of a number of high quality trials which have impacted on practice both nationally and internationally
- A good publication record in high impact journals and presentation record at international meetings
- A good track record with funding applications
- The development of a translational programme which is beginning to yield data
- Excellent international standing
- A strong history of international collaboration, with major membership of GCIG
- Good links with the BGCS
- Productive links with three CTUs through which most of the gynae trials are run
- The establishment of roadshows to try and improve recruitment in poorly recruiting areas of the country
- National trials meetings

Issues for the CSG to consider:

- The balance of translational work within its portfolio
- The key translational questions to be asked from banked specimens and how to assure that these take maximal advantage of the research opportunities
- The key questions which follow on from current PARP studies/anti-angiogenesis trials
- What are the new clinical questions in endometrial cancer and cervical cancer
- What strategies other that neo-adjuvant therapy should be used in cervical cancer
- The balance of phase II vs phase III trials in the portfolio
- How best to link up with ECMCs and radiation biologists
- The potential impact of commercial studies and how these can best be used to leverage access to novel agents for academic studies
- How best to use consumer input and the role they can play in linking up with patient charities and publicising trials
- How best to develop and use the proposed gynae leads in each of the fifteen new CRNs
- The role of hub and spoke mechanisms in trial delivery