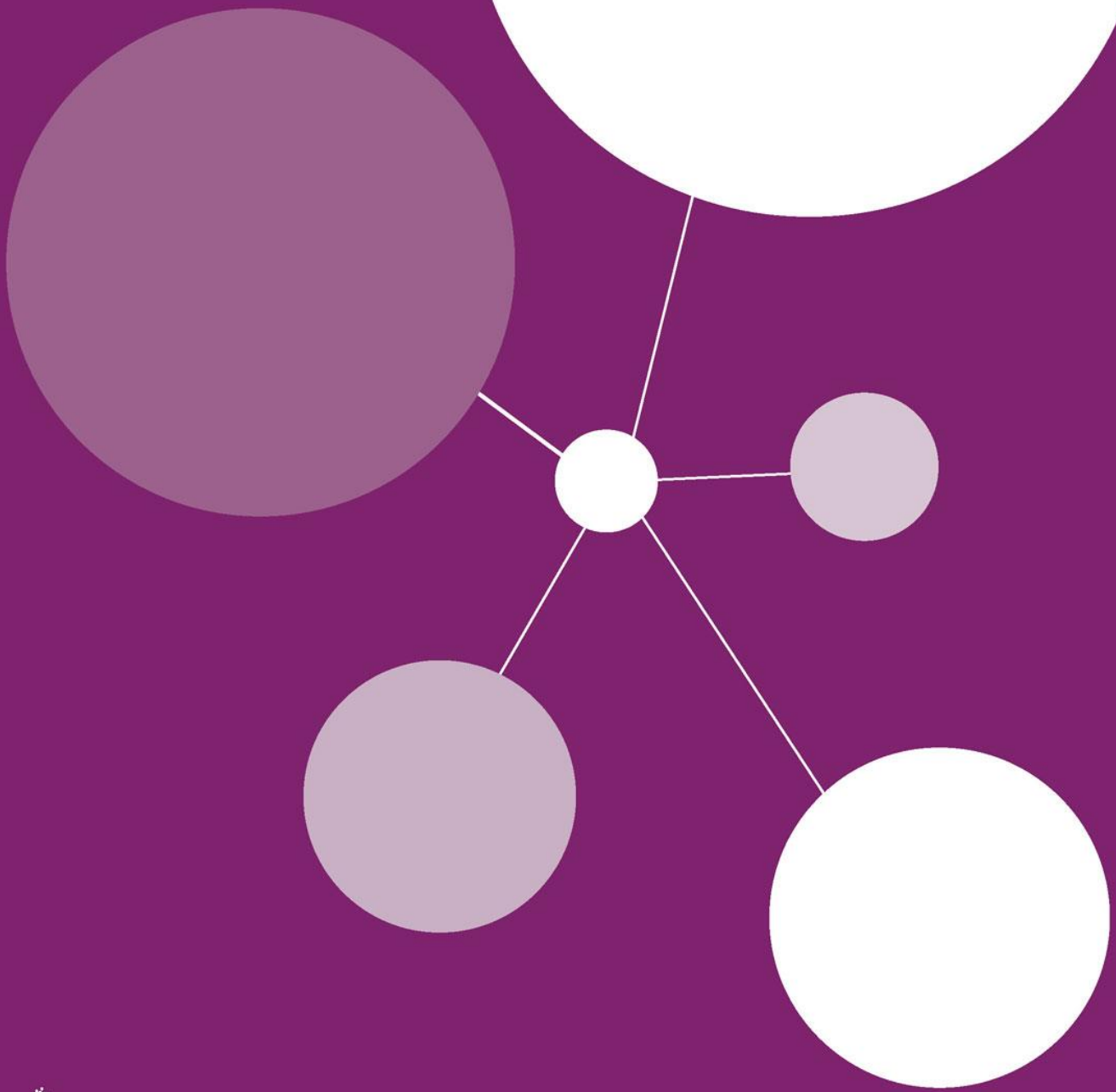
NCRI
National
Cancer
Research
Institute

NCRI Breast Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Breast Cancer CSG Annual Report 2014/15

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

The NCRI breast cancer trials portfolio remains strong with 39 new studies opening matching the closure of 39 studies. The portfolio covers a wide range of studies across multiple aspects of breast cancer research. The Breast CSG has noted the reduction in numbers of patients recruited to clinical trials. This is common to all common cancer groups and is a consequence of increasing levels of stratification within the umbrella of breast cancer, with trials focusing increasingly on specific subgroups rather than having a wide eligibility. The recent increase in numbers of trials open is a reflection of this trend. A major challenge is to ensure a balanced portfolio of large pragmatic studies but to also support the development of inevitably more complex cutting edge molecularly driven research. The group aims specifically to promote increased surgical research and encourage a clinical trials based culture within the whole health care team delivering breast cancer services.

Notable successes this year include:

The successful completion of the OPTIMA pilot study this has demonstrated the feasibility of randomising patients to chemotherapy or to a molecular signature driven decision to omit or give chemotherapy. The phase III OPTIMA study is planned to open to recruitment in 2015/16.

The ARTEMIS study published in Lancet Oncology demonstrated that pathological complete response is increased by the addition of bevacizumab to neoadjuvant chemotherapy. This study has largely settled an ongoing controversy confirming the benefit is largely confined to triple negative breast cancer. This study has rejuvenated interest in understanding the discordance between neoadjuvant and adjuvant outcomes in this setting.

Two national surgical trials have opened, LORIS the first trial to attempt to reduce overtreatment in screen detected or asymptomatic DCIS; and POSNOC, a trial designed to determine the optimal management of positive sentinel lymph node biopsy, again a trail aimed at reducing morbidity.

In the advanced disease setting the TNT study has generated practice changing findings demonstrating superior activity and tolerability of platinum agents in BRCA associated metastatic breast cancer. In addition, the study has identified additional molecular subgroups within the triple negative category with differential sensitivity to platinum and taxanes. This study is an example of a pragmatic design with inbuilt and pre-specified molecular subgroup analysis. The combination delivering a definitive answer in one area and providing hypothesis generating data triggering further detailed subgroup analysis which is underway.

Finally the PALOMA III study sponsored by Pfizer with a UK CI (Nick Turner) has demonstrated clear advantage to the addition of palbociclib CDK 4-6 inhibitor to endocrine therapy in ER positive MBC. The study was halted early reaching predefined positive endpoints and has already resulted in accelerated registration of palbociclib in the USA.

2. Structure of the Group

Dr Daniel Rea has taken over as The Chair of the CSG from Professor Alastair Thompson. New members of the CSG are Dr Andrew Wardley, Professor Arnie Purushotham, Dr Carolyn Taylor and Professor Janet Brown

Ms Adele Francis has joined the main CSG in her capacity as Royal College of Surgeons breast cancer subspecialty research lead.

Dr Deborah Fenlon has joined the main CSG as Chair of the Symptom Management Working Party.

We have appointed two trainee representatives Dr Ciara O'Brien and Ms Shelly Potter.

3. CSG & Subgroup strategies

Main CSG

While the Breast CSG has not previously articulated a strategy it should be noted that the CSG activity has been closely aligned to the emerging strategy outlined in Appendix 2.

Translational & Imaging Subgroup (Chair, Dr Abeer Shaaban)

The Translational & Imaging Subgroup reviewed and provided feedback on trials with translational aspect and also on relevant Registration of Concept studies. The subgroup has addressed barriers to translational research and provided guidance for pathologists and clinicians. Key achievements of the subgroup include:

1. Addressing the variation in practice of handling and reporting breast surgical specimens following neoadjuvant chemotherapy. Neoadjuvant chemotherapy trials are increasing with a real need for standardisation of pathological handling and reporting. The Subgroup provided recommendations on macroscopic and microscopic examination of those specimens, reporting systems and current evidence regarding the rates and significance of pathological response. This was published in Histopathology (Pinder et al 2015 Jan 14. doi: 10.1111/his.12649)

2. One of the issues hindering research and trials into inflammatory breast cancer is the inconsistency of criteria for diagnosis. Members of the Subgroup have contributed to developing guidance on criteria for diagnosis and management of this rare but aggressive breast cancer. Following publication of the guidelines (Rea et all, Br J Cancer 2015), members of the Subgroup contributed to a UK Inflammatory Breast Cancer Consortium and an international meeting was hosted on 24/4/15 to plan UK and international collaboration with prospective tissue collection for research and trials into IBC. The tissue collection is being supported by Breast Cancer Campaign.

3. Following on from the work that the Subgroup conducted on addressing barriers to molecular testing and proposal of clinical pathways (Shaaban et al J Clin Pathol 2014), this multidisciplinary group, including patient representation, has provided a view point on timely availability of test

results for discussion at the MDT meetings. This has been submitted for publication to EJSO (Francis et al).

4. The Subgroup has discussed and provided input into a number of high calibre trials with translational component. These have now been successfully funded. They include (LORIS, CI: Adele Francis, member of the Subgroup, OPTIMA, CI: Rob Stein, member of the Subgroup). The design and initial analyses were presented at international level including the NCRI meeting, Liverpool 2014 and San Antonio Breast Cancer Symposium 2014, see list of subgroup publications.

5. The Subgroup has updated its membership to include two experienced radiologists to address relevant imaging issues. Work is underway to look into the quality and methods of image acquisition for MRI assessment. The Subgroup currently includes a core patient member who provides invaluable input into both translational and imaging issues from patient prospective.

Early Disease Subgroup (UK Breast Intergroup) (Chair, Professor Judith Bliss)

The Early Disease Subgroup has continued to coalesce this year and held its second annual strategic development day in Feb 2015. The group is pleased to note the successful funding/launch of several important trials this year including NIHR HTA support for the OPTIMA, LORIS and POSNOC and PARTNER trials. The Subgroup undertook a scoping exercise across the portfolio and has identified various areas of unmet clinical need which would be suitable for research. Types of trial proposed include pragmatic trials to obtain evidence to inform current surgical practice, trial platforms and trials which will intervene based on novel biomarker signal. Clinical areas discussed include the role of sentinel lymph node biopsy after neoadjuvant chemotherapy and the need to tailor antiHer2 therapy according to residual risk after neoadjuvant treatment.

The Subgroup also continues to engage with the wider breast cancer research community and facilitate discussions of trial concepts via the bi-annual meetings of the UK Breast Intergroup. This year has seen the formalisation of feedback for UKBI presentations ensuring the overall essence of the group feedback is captured and enabling the CSG to be informed of prior discussions. Notable proposals discussed at UKBI this year include the tracking of ctDNA post neoadjuvant treatment in patients with triple negative disease with intervention based on detection of specific mutations and plans to build on the success of the POETIC trial to establish a trial platform in the perioperative setting for biological evaluation of agents involved in endocrine resistance.

Advanced Disease Subgroup (Chair, Dr Alistair Ring)

The Advanced Disease Subgroup oversees a large portfolio of therapeutic interventional trials. Key achievements of the subgroup include:

1. Delivery of a large trial portfolio (34 trials currently open or in the process of opening according to the metastatic portfolio map). This portfolio is well balanced with good representation of trials in all disease subgroups (defined by ER status, HER-2 status and BRCA mutation status). This maximises the likelihood that patients with advanced disease will be potentially eligible for a clinical trial.

2. The results of the TNT trial (a randomised phase 3 trial of Carboplatin compared with Docetaxel for patients with advanced triple negative or BRCA1/2 mutated breast cancer) was

presented at the San Antonio Breast Cancer Symposium (2014) by Professor Andrew Tutt. This was a UK-led academic study whose findings have significant implications for both women with triple negative breast cancer but also particularly for those women with BRCA mutation associated breast cancer.

3. The plasmaMatch study has been approved for funding by CTAAC. This is a highly innovative trial in which 1000 patients across the UK will undergo circulating tumour DNA screening and those with targetable mutations entered into downstream trials. This innovative approach will provide a platform for access to targeted treatments across the UK. The study involves collaborations with AstraZeneca and Puma but there is the potential for further collaborations to be established based on the use of this screening platform.

4. UK investigators continue to contribute at an international level to industry sponsored studies. Dr Nick Turner (member of the Subgroup) presented the results of the PALOMA-3 trial at ASCO on 1st June 2015 (with simultaneous publication in the New England Journal of Medicine).

4. Task groups/Working parties

Symptom management working party

The Working Party was initiated in May 2013 via the patient representative on the NCRI Breast CSG to establish a group to consider research into symptoms that affect women with breast cancer. The remit was set initially to focus on hot flushes and night sweats; this is now to broaden out to include other symptoms. Chairmanship of the group has passed from Dr Adrienne Morgan to Dr Deborah Fenlon. The group has been kindly hosted by Baroness Delyth Morgan, Chief Executive of Breast Cancer Campaign, at the House of Lords.

The working party's initial focus was to raise awareness of hot flushes in women with breast cancer, explore current knowledge and stimulate new research into this field.

Outputs

We have:

- Undertaken rapid surveys into current knowledge and management of hot flushes with patients, primary and secondary care health professionals.
- Acted as consultants to NICE guidance on menopause management
- Presented posters at six conferences and oral presentations at five conferences
- Presented a symposium on breast cancer at the European Menopause and Andropause Society conference 2015
- Written four papers for publication
- Drafted eight outline proposals to go to the Breast Cancer Campaign Hub: Two have been shortlisted:
    - Acupuncture for menopausal symptoms following breast cancer treatment. Brett, Filshie, Morgan, Fenlon, Watson and Turner
    - Using fMRI to predict treatment outcome of flushes in women with breast cancer using tamoxifen. Sassarini, Lumsden, Hunter
- Stimulated and supported the development of studies into acupuncture, CBT, adherence to hormone therapy, vaginal pessaries, and the use of megace for hot flushes in breast cancer.

- The Working Party have identified researchers into the biology of vasomotor symptoms and new researchers in this area who will pursue this avenue for future research. Several studies are currently in development.

The Working Party will be undertaking a strategy meeting in June 2015 to review their portfolio and set direction for future working.

5. Patient recruitment summary for last 5 years

In the Breast CSG portfolio, 39 trials closed to recruitment and 39 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	29384	4832	5078	4574	11.8	10.6
2011/2012	33914	5483	8428	4772	19.6	11.1

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	20257	11940	7154	6594	14.6	13.5
2013/2014	12148	5973	4642	5888	9.5	12.0
2014/2015	11417	5109	6042	3146	12.3	6.4

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

The CSG receives updates from SPED and CTRad through cross representation and discussions have taken place with the Chair of the Supportive & Palliative Care CSG. A strategic aim is to foster better cross referencing and joint working with these groups.

The encouragement of surgical research initiatives is a strategic priority for the CSG and aims to engage the largest group of breast cancer clinicians in furthering breast cancer research. To this end the CSG has been supporting the very encouraging activities of the Royal College of Surgeons in promoting a research culture within the trainee environment engaging with the College in a breast surgical trials day and a 2 day tomorrow's leaders course for all surgical trainees with specialty specific workshops in breast cancer research.

International links are maintained through regular attendance by the Chair and Professor Bliss at Breast International Group (BIG) meetings. The UK is participating in a number of BIG studies and is actively engaged in discussion with BIG in setting up new studies. Professor Cameron acts as link between the Breast CSG and EORTC. The UK will open 12 sites to the Aurora Study a BIG initiative to characterise metastatic breast cancer through targeted whole genome sequencing and act as a feeding platform to downstream intervention trials for tumours with identified drugable targets.

The Chair and Subgroup Chairs attended the subspecialty leads meeting in March and the subspecialty leads attended the CSG strategy day in May. The strategy in development represents a joint strategy initiative developed with the CSG and subspecialty leads. Inexperienced subspecialty leads are being encouraged to attend a CSG meeting to familiarise them with the CSG functions.

7. Funding applications in last year

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
BLUEBELL: A proof of concept phase II study of buparlisib in her2 positive breast cancer with brain metastasis following her2 directed monoclonal antibody therapy	Feasibility application	Professor Carlo Palmieri	Resubmission requested
Pre-NOSTRA: A feasibility study for the planned phase III no surgery trial (NOSTRA)	Feasibility application *Resubmission*	Miss Adele Francis and Professor Daniel Rea	Not funded
PARTNER: Platinum and PARP inhibitor for neo-adjuvant treatment of triple negative and/or BRCA positive breast cancer	Outline application	Drs Jean Abraham & Helena Earl	Full application invited
Trans-POSNOC: A biomarker study for axillary recurrence in early stage breast cancer patients with a positive sentinel lymph node biopsy	Sample collection application	Miss Beatrix Elsberger	Not funded
Trans-PERSEPHONE and Trans-PERSEPHONE-SNPs: The pharmacogenomics and pharmacogenetics of adjuvant trastuzumab	Sample collection application *Extension*	Professor Carlos Caldas	Funded
November 2014			
FEASIBILITY of IBIS 3: POLaR. An International Breast Intervention Study investigating Prevention Of Late Recurrence in ER+ breast cancer survivors following 5 years of adjuvant treatment	Full Application	Professor Jack Cuzick	Achieved fundable score – endorsement offered
IBIS II Prevention and IBIS-II DCIS Extension	Full Application *Extension*	Professor Jack Cuzick	Funded
PARTNER: Platinum and PARP Inhibitor for Neo-adjuvant treatment of Triple Negative and/or BRCA positive breast cancer	Full Application	Dr Jean Abraham/Dr Helena Earl	Achieved fundable score – endorsement offered
BELLE-CNS: A proof of concept phase II study of Buparlisib in HER2 positive breast cancer with brain metastasis following HER2 directed monoclonal antibody therapy	Feasibility Application	Professor Carlo Palmieri	Achieved fundable score – endorsement offered
plasmaMATCH: A multiple parallel cohort, non-	Outline	Dr Nicholas	Full

randomised, open label, multi-centre phase IIa clinical trial aiming to provide proof of principle efficacy for designated targeted therapies in patients with advanced breast cancer where the targetable mutation is identified through ctDNA screening	Application	Turner	application invited
March 2015			
A multiple parallel cohort, non-randomised, open label, multi-centre phase IIa clinical trial aiming to provide proof of principle efficacy for designated targeted therapies in patients with advanced breast cancer where the targetable mutation is identified through ctDNA screening	Full application	Dr Nicholas Turner	Funded
Magnetic Occult Lesion Localization (MOLL) in the Management of Non-palpable Breast Cancer	Feasibility application	Mr Michael Douek	Not funded
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Can early breast cancer patients safely avoid surgery following pathological Complete Response from neo-adjuvant chemotherapy and dual anti-HER2 therapy? The NOSTRA trial.	HTA outline	Ms Adele Francis	Not Funded
OPTIMA: Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis	HTA full application	Dr Robert Stein	Funded

8. Collaborative partnership studies with industry

The CSG has extensive interaction with industry. Several current registration studies have UK Chief Investigators. The majority of industry studies are conducted as fully sponsored studies with NCRN endorsement but we also have two industrial partnerships.

Both partnership and Industry studies are predominantly within the setting of metastatic breast cancer with a small number focused in the neoadjuvant/adjuvant setting as window studies therapeutic neoadjuvant and adjuvant studies. The only area where industry studies dominate the portfolio is in the metastatic setting, where numerically industry studies make up 60% of the portfolio with the remainder partnership or academic studies

The Breast CSG has an established partnership with Astra Zeneca with a range of studies in the neoadjuvant and metastatic setting covering multiple targeted agents. This successful partnership is ongoing with new proposals under consideration.

A new collaborative alliance has been forged with Pfizer in 2015 the first meeting was a arranged as a virtual Webinar/teleconference focusing on new opportunities with palbociclib expressions of interest are being explored with Pfizer.

9. Impact of CSG activities

Several trial results have had practice changing impact on breast cancer management.

The START trials of radiotherapy fractionation have had significant influence on worldwide radiotherapy fractionation with many guidelines now recommending the hypofractionated 40Gy in 15 fractions over longer fractionations resulting in cost savings and convenience to patients with no loss of efficacy. The AMAROS trial has provided data suggesting nodal irradiation is as effective as axillary surgery and is endorsed as an option for management of a positive axilla in the 2015 St Gallen Consensus Statement.

The AZURE trial which demonstrated the activity of adjuvant bispohosphonates in postmenopausal women has now been strengthened with a metanalysis now in press confirming these findings including an emerging survival impact. Adjuvant bisphosphonates recommendations are currently being considered by the Clinical reference group updated ASCO and NCCN guidelines are expected following publication of the metanalysis.

The ATLAS and aTTom trials have demonstrated the efficacy advantage of extending adjuvant tamoxifen to 10 years in treatment of ER positive early breast cancer. The recommendation for extended adjuvant tamoxifen from 5 to 10 years in selected women with breast cancer is included in the 2015 St Gallen Consensus statement.

The CSG has provided commentary to all breast cancer applications to CTAAC.

The CSG has led the joint response from the NCRI and RCP to NICE breast cancer technology appraisals and reviews and provided expert testimony through nominated CSG members.

10. Consumer involvement

Excellent engagement and collaboration occurs between the consumers and health professionals across the CSG and subgroups. Consumer points are listened to and opinions sought. Representation occurs at each meeting and support been available where needed. This has been of particular importance in the past year where that has been only one consumer representative for the majority of the year.

Consumer communication between the breast study groups helps to provide a more holistic view from a lay perspective.

Consumer involvement within the UKBI is fully embedded ensuring that there is always a voice when needed.

Strong consumer representation remains a very strong driving force behind the Symptom Management working party through individual membership, ICPV as co-opted members and Breast Cancer Now, who provide secretariat support and facilities for meetings including refreshments. Ongoing work will ensure this strong consumer involvement becomes embedded in the vision and terms of reference for the group.

11. Open meetings/annual trials days/strategy days

The annual trials day was held on March 5th 2015 at Church House, Westminster. Attended by 250 delegates with a proportionally larger number of clinicians attending compared to previous meetings, the theme for the day was personalised medicine in breast cancer. Keynote speaker Professor Carlos Caldas described the most recent developments in molecular taxonomy of early breast cancer. This was accompanied by a clinical commentary from Dr Alistair Ring and a research nursing perspective to the description, management and documentation of new side

effects from novel therapies from Cathryn and Lorraine Turner from the Christie Hospital. Recent successes from UK trials were presented with the TNT trial and the ARTEMIS and OPTIMA trials were presented by Professor Tutt, Dr Earl and Dr Stein. New personalised medicine studies in the form of the ROSCO study and plasmaMatch were highlighted. Presentations on the surgical trials initiatives and the role of the RCS breast cancer subspecialty lead in promoting surgical research was provided by Ms Adele Francis.

A strategy development day was held in May 2015 attended by CSG and members and regional subspecialty leads. At this meeting strategic aims have been agreed the rollout to a completed strategy document is underway.

A meeting of stakeholders was hosted by CRUK in September 2014 to explore the research opportunities in breast screening. A more complete understanding of the potential utility of combining genetic and environmental factors in risk prediction models is needed. An application from the Cambridge epidemiology group to develop these is currently under funding consideration

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

The implementation of strategy for the Breast CSG is an ongoing workstream. We have a programme of pragmatic randomised trials opening or in development as well as a programme of more ambitious projects bringing cutting edge molecular techniques into the NCRI portfolio, examples of the former being the POSNOC, Add Aspirin study and, Mammo 50 and a range of studies in development including radiotherapy and surgery trials. Complex molecular studies in development such as the International AURORA and National plasmaMatch studies demonstrate a commitment to personalised medicine. We are engaged with the surgical community through The Royal College of Surgeons, and Association of Breast Surgeons in developing a research culture within the current generation and looking to the next generation of surgical researchers through our support to trainee led breast cancer research collaboratives. Our consumer representation extends far beyond the two CSG representatives with consumer involvement in the development of trial ideas and nominated consumer representation in individual trial development groups from inception through to completion.

13. Priorities and challenges for the forthcoming year

Priorities for the Breast CSG in the coming year are:

National Surgical Trials

Delivery on the two national surgical trials POSNOC and LORIS are twin priorities. POSNOC is now recruiting, albeit slightly behind target but bringing on more centres. LORIS has almost completed the set up phase of the feasibility component. Recruitment is currently on target but will require accelerated recruitment to maintain an encouraging start. It is intended for at least one more national surgical trial to secure funding in the next year.

Breast Cancer GeCIP

Rollout of the Breast cancer GeCIP Domain is a key priority for 2015/16. The CSG submitted a bid for the breast cancer domain which was scored highly and a GeCIP consortium has been formed to take this work forward. The GeCIP Group is led by Dr Nicholas Turner with support from geographically widely spread Gen Somic medicine centres sample collection is scheduled to

commence in 2015. The Group is working hard to define the spectrum of sample collections which will focus primarily on new samples but use of some historic series or clinical trial archives with well annotated clinical outcomes are not excluded. The organisation of the processes and delivery Interpretation of the genomic data is a major workstream.

Clinical trial recruitment

High recruitment to a broad portfolio of clinical trials remains the lifeblood of healthy clinical research environment identification and assistance to under recruiting studies remains an ongoing priority for the CSG. Encouragement to new investigators to participate in research the CLRN subspecialty leads will be utilised to bring issues to the CSG and we intend to maintain the two way dialogue to understand how we can learn from these leads about the research priorities of the investigator community.

Challenges for the CSG include:

Maintaining recruitment across the portfolio

The trend in the breast trials portfolio is for trials to become increasingly complex and to focus on more closely defined subgroups or specific problems encountered in limited circumstances. In the current cost conscious NHS environment the delivery of a more complex clinical trial portfolio and maintenance of current or past recruitment levels is a challenge across all tumour sites with breast cancer no exception. All breast units will need to actively engage in clinical trials based in molecular sub-classification and be prepared to open studies in niche areas where recruitment numbers in each centre will be low.

Encouraging intersite collaboration

The AURORA and plasmaMatch studies are molecular profiling studies which will identify molecular phenotypes within metastatic breast cancer. These studies, which will be opening over the next year, will bring into sharp focus the requirement for access to a range of downstream trials currently in development to explore the utility of a genomic sequencing approach to improve breast cancer treatment for metastatic disease. The AURORA and plasmaMatch trials will initially be opening at sites capable of running downstream phase II trials they are unlikely to be able to maintain a full portfolio of trials as these expand. The solution is to build regional networks which are capable of supporting a full portfolio. These already exist to some extent within some areas as informal arrangements but this is patchy and better developed in areas of population density and dependent on individual to individual collaboration. It would be beneficial for these arrangements to be formalised and trials for rare subtypes to be set up strategically in geographic and demographic locations to encourage network formation that permits widespread access to trials for patients with uncommon phenotypes. Patients are likely to be asked to travel further to get access to appropriate trials. Work with patient groups will be required to educate and encourage patients to be prepared to move to a new hospital to maximise the options for treatment within clinical trials. The above two trials will provide a platform to explore the setting up of local/regional collaborative working.

New models for PIC site and trial site interaction

The current arrangements for PIC site working limits the activity of the PIC site to identification procedures such as a blood test or submission of a tumour sample to a trial site. This often means repeating investigations. There is potential for the role of the PIC site activity to be

expanded to completion of consent and screening and pre-trial procedures such as tumour biopsy, thus avoiding overloading the trial site infrastructure and avoiding unnecessary travel for patients. This will require excellent communication and collaboration between sites will challenge conventional R&D and clinical governance practices. This type of enhanced collaboration probably needs to be approached as an evolutionary process designed around specific trials but from which good practice examples may be used to inform how to implement and embed such collaboration on a wider scale. We hope to provide examples of good working practice here and develop a proposal to bring to the CSG Chairs' Forum to harmonise development of this concept.

14. Concluding remarks

Clinical research in breast cancer in the UK is producing practice changing clinical trial results with a wide range of trials and research endeavour across most aspects of breast cancer. We are in the midst of an exit phase of transition into the arena of molecular genomics as a driver of clinical research but this endeavour is not at the exclusion of more traditional trial methodology and a large place remains for the pragmatic randomised trial to answer specific practical questions. The CSG is committed to supporting this broad based approach to clinical trials. We have within the CSG a wide range of experience and expertise and particularly strong consumer representation both within and allied to the group membership.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Translational & Imaging Subgroup Strategy
- C – Early Disease Subgroup (UK Breast Intergroup) Strategy
- D – Advanced Disease Subgroup 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 Breast CSG 2014 Progress Review

Dr Daniel Rea (Breast Cancer CSG Chair)

Appendix 1

Membership of the Breast CSG

Name	Specialism	Location
Ms Shelley Potter*	Clinical Lecturer in General Surgery	Bristol
Professor David Cameron	Clinical Oncologist	Edinburgh
Dr Charlotte Coles	Clinical Oncologist	Cambridge
Dr Andreas Makris	Clinical Oncologist	Middlesex
Dr Carolyn Taylor	Clinical Oncologist	Oxford
Mrs Katrina Randle	Consumer	Leeds
Mrs Hilary Stobart	Consumer	Nottingham
Dr Elizabeth Mallon	Histopathologist	Glasgow
Professor Janet Brown	Medical Oncologist	Sheffield
Dr Ellen Copson	Medical Oncologist	Southampton
Dr Helena Earl	Medical Oncologist	Cambridge
Dr Iain Macpherson	Medical Oncologist	Glasgow
Professor Carlo Palmieri	Medical Oncologist	Liverpool
Dr Daniel Rea (Chair)	Medical Oncologist	Birmingham
Dr Alistair Ring	Medical Oncologist	Brighton
Professor Peter Schmid	Medical Oncologist	Brighton
Dr Nicholas Turner	Medical Oncologist	London
Dr Andrew Wardley	Medical Oncologist	Manchester
Dr Abeer Shaaban	Pathologist	Birmingham
Dr Emma Harris	Radiologist	London
Professor Iain Lyburn	Radiologist	Cheltenham
Dr Ciara O'Brien*	Specialist Registrar Medical Oncology	Manchester
Professor Judith Bliss	Statistician	London
Ms Adele Francis	Surgeon	Birmingham
Professor Chris Holcombe	Surgeon	Liverpool
Mr Stuart McIntosh	Surgeon	Belfast
Professor Arnie Purushotham	Surgeon	London

* denotes trainee

Membership of the Subgroups

Translational & Imaging Subgroup		
Name	**Specialism**	**Location**
Mrs Hilary Stobart	Consumer	Nottingham
Dr Rob Stein	Medical Oncologist	London
Professor John Bartlett**	Pathologist	Ontario
Professor Fiona Gilbert	Radiologist	Cambridge
Professor Iain Lyburn	Radiologist	Cheltenham
Professor Sarah Pinder	Pathologist	London
Dr Colin Purdie	Pathologist	Dundee
Dr Emad Rakha	Pathologist	Nottingham
Dr Abeer Shaaban (Chair)	Pathologist	Birmingham
Dr Val Speirs	Pathologist	Leeds
Professor Janet Dunn	Statistician	Warwick
Ms Adele Francis	Surgeon	Birmingham
Professor Alastair Thompson**	Surgeon	USA

Early Disease Subgroup (UK Breast Intergroup)		
Name	**Specialism**	**Location**
Dr Charlotte Coles	Clinical Oncologist	Cambridge
Professor Andrew Tutt	Clinical Oncologist	London
Mrs Katrina Randle	Consumer	Leeds
Dr Andrew Wardley	Medical Oncologist	Manchester
Dr Deborah Fenlon	Senior Research Fellow	Southampton
Professor Judith Bliss (Chair)	Statistician	London
Mr Peter Barry	Surgeon	London
Dr Cliona Kirwan	Surgeon	Manchester
Mr Anthony Skene	Surgeon	Bournemouth

Advanced Disease Subgroup		
Name	**Specialism**	**Location**
Dr Mark Beresford	Clinical Oncologist	Bristol
Dr Adrian Harnett	Clinical Oncologist	Norfolk
Dr Andreas Makris	Clinical Oncologist	Middlesex
Dr Duncan Wheatley	Clinical Oncologist	Cornwall
Ms Elizabeth Benns	Consumer	Letchworth
Ms Mairead MacKenzie	Consumer	
Mrs Katrina Randle	Consumer	Leeds
Dr Anne Armstrong	Medical Oncologist	Manchester
Professor Rob Coleman	Medical Oncologist	Sheffield
Dr Alistair Ring (Chair)	Medical Oncologist	Birmingham
Dr Rebecca Roylance**	Medical Oncologist	London
Professor Peter Schmid	Medical Oncologist	Brighton
Dr Nick Turner**	Medical Oncologist	London
Dr Cath Harper-Wynne	Medical Oncologist	London

*denotes trainee

**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The strategic aims of CSG are organised in hierarchical order with the primary aim being to improve the outcomes and experience of breast cancer patients and those at risk of developing breast cancer

Secondary order aims are to:

1. Ensure that all breast cancer patients have opportunity to take part in research with access to a wide range of studies
2. Increase patient expectation of being involved in a clinical trial
3. Ensure equality of access for all patients through developing appropriate referral pathways and extended PIC sites for complex studies
4. Embed a research culture across the entire patient pathway within all healthcare professionals and in all institutions providing breast cancer services
5. Optimise trial design to adequately answer specific questions within the confines of the current and future health care environment
6. Empower and educate patients and the public to drive a research oriented culture within the provision of routine care
7. Increase the number of local PIs participating in clinical trials
8. Increase the level of access to and use of tissue from all patients throughout the patient pathway
9. Educate all healthcare professionals on the advantages of recruiting patients to trials
10. Improve International collaboration where appropriate and key to the success of a trial
11. Strengthen links with other NCRI CSGs, HCIS, advisory groups and CTRad
12. Strengthen links with groups and alliances which impact on the ability to deliver trials
13. Ensure a balanced portfolio of clinical trials with appropriate mix of complexity to allow full exploitation of clinical trial expertise and capacity
14. Encourage the documentation of research initiatives and research competencies and achievements of all breast cancer clinicians as a
15. Disseminate trials information and availability through regional subspecialty leads to enhance recruitment
16. Deliver the commercial and non-commercial portfolio
17. Develop more joined up and robust processes to respond to requests for peer review

B – Translational & Imaging Subgroup Strategy

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To identify future translational opportunities for inclusion within portfolio studies To work with the early and late subgroups to design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk in early disease . Explore opportunities for identifying cross cutting translational themes across the portfolio & for coupling / decoupling studies where appropriate Encourage a uniform minimum standards across all MDTs for the extent and timing of pathological information including standard mutational analysis and biomarker evaluation through guideline and position paper publications Encourage uniform minimum standards for reporting and decision making within MDTs based on comprehensive and timely imaging and biomarker information including a requirement to identify and record potential trial eligibility	All AS AF/SP	Ongoing
1b. Portfolio development imaging	Ensure /advise on appropriate protocols for imaging in portfolio studies identify opportunities for assessment of novel imaging research	IL/FG	Ongoing
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to risk & likely benefit To promote use of informative experimental models including focussing novel treatment evaluation to those with residual – assessable - disease • post neoadjuvant – macroscopic / microscopic (ctDNA) • adjuvant – microscopic (ctDNA) • window of opportunity – biological endpoints • Metastatic disease – plasma detectable ctDNA; disease accessible for biopsy		Ongoing

Strategic objective	Activity	CSG Lead	Date
1d integrated Imaging and translational research within the breast portfolio	Promote and advise on the integration translational and imaging research into all trials where possible to include • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease • Appropriate imaging modalities for all trials • Novel imaging (as subprotocol if appropriate) in clinical trials Develop virtual Biobank through cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc	NT	
2 Collaborative approach to developmentt of translational research	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive translational elements to portfolio studies Harnessing expertise and linking people with related skills to maximise & quality of translational input to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (e.g. genomic information multiple biopsies data protection) • Arrange forums for discussion • Ensure PPI representation at meetings Engage with Royal College of Surgeons and Association of Breast Surgery (via Adele Francis) and to support initiatives to increase the number of surgical trainees involved in clinical trials research Maximise opportunities for international translational collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All HS All AS DR DC JB	

Strategic objective	Activity	CSG Lead	Date
3. Improving trials methodology & clinical utility	Endeavour to identify new predictors of risk and outcome. • able to identify/predict patients with residual disease risk • Able to predict sensitivity/insensitivity to therapeutic intervention Engage with trials methodologists and bioinformaticians to ensure trials are designed so that translational data is exploited effectively and fully	NT AS/JB	Ongoing

PB	Rob Stein
JB	John Bartlett
FG	Fiona Gilbert
IL	Iain Lyburn
SP	Sarah Pinder
CP	Colin Purdie
ER	Emad Rakha
AS	Abeer Shaaban
VS	Val Spiers
JD	Janet Dunn
AT	Alistair Thompson
AF	Adele Francis
HS	Hillary Stobart

C – Early Disease Subgroup (UK Breast Intergroup) Strategy

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To horizon scan the portfolio to identify future gaps & to develop trial concepts for discussion within such areas To design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk Explore opportunities for identifying cross cutting themes across the portfolio & for coupling / decoupling studies where appropriate	Subgroup	Ongoing
1b. Portfolio development (local therapy)	Explore opportunities for Surgery / RT technology evaluation • new technologies • extent of treatment • need for treatment	CC / AT PB / AS / CK	Ongoing
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to risk & likely benefit To promote use of informative experimental models including focussing novel treatment evaluation to those with residual – assessable - disease • post neoadjuvant – macroscopic / microscopic (ctDNA) • adjuvant – microscopic (ctDNA) • window of opportunity – biological endpoints • Metastatic disease – plasma detectable ctDNA; disease accessible for biopsy To promote development of pragmatic trials to test residual unanswered treatment questions within context of contemporary trial design (exploring alternative routes for collecting follow up data – see below, incorporating PROMS collected digitally (e.g. via Web, App), serial monitoring for micrometastatic disease), e.g. • Choice of regimen (efficacy vs tolerability) • Duration • Sequencing of treatments	AT – PHOENIX – post neoadjuvant residual disease wop platform AW – her2+ modulating treatment according to risk JMB / DC / AR – pragmatic CT trials	Ongoing

Strategic objective	Activity	CSG Lead	Date
1d Portfolio development integrated (translational research)	Promote expectations for integrating translational research into all trials where possible (patient acceptability / cost considerations) • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease Develop virtual Biobank (guided by Translational subgroup) • cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc.	NT	
2 Collaborative approach to trial development & participation	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive studies • National Breast Trialists Day • UK Breast Intergroup meetings 2x/year • UK Breast Intergroup Feasibility & interest surveys Harnessing expertise and linking people with related ideas (UKBI) – to maximise efficiency & quality to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (eg multiple biopsies) • Arrange forums for discussion • Ensure PPI representation at meetings • Aim to optimise efficiency in and minimise inconvenience to PPI representatives in relation to workload management Engage with Royal College of Surgeons and Association of Breast Surgery (via Adele Francis) and to support initiatives to increase the number of surgical trainees involved in clinical trials research Link with CTRad to expand RT studies Maximise opportunities for international collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All KR MM All CC JB DR DC	

Strategic objective	Activity	CSG Lead	Date
3. Improving trials methodology & clinical utility	Endeavour to identify new predictors of risk and outcome intermediate endpoints • aimed at being true surrogates of long term disease outcomes (DFS, OS) • able to identify/predict patients with residual disease risk Collaborate with NCIN (inc Breast SSCRG) and CRS to validate completeness and accuracy of data acquired from routine data sources with a view to replacing hospital based follow up for disease outcome Engage with trials methodologists for optimising trial designs efficiently – multiple questions within 1 trials (couple / decouple studies).	NT - Post neoadjuvant ctDNA mutation identification & monitoring for disease risk JB – NCIN Validation project / with breast SSCRG	F 2015, then annual

PB	Peter Barry
JB	Judith Bliss
DC	David Cameron
CC	Charlotte Coles
DF	Debbie Fenlon
CK	Cliona Kirwan
KR	Kat Randle
AR	Alistair Ring
AS	Anthony Skene
NT	Nick Turner
AT	Andrew Tutt
AW	Andrew Wardley

D – Advanced Disease Subgroup Strategy

(i) There remain a number of challenges in the delivery and development of the academic portfolio in the UK. One of these is the challenge of delivering the commercial trial portfolio whilst maintaining the presence of academic studies. Commercial trials are adopted onto the metastatic portfolio assuming they achieve minimal criteria and this can mean that there is less room for locally initiated academic studies. There are notable exceptions (the MANTA study and PAKT studies, chief investigator Professor Peter Schmid) and the plasmaMatch study previously discussed. Nonetheless this is an area requiring close observation to ensure that the continued academic presence of the UK breast cancer community on the international scene. Bearing this in mind the Advanced Disease Subgroup is developing a strategy which involves working more as a protocol development group rather than what has hitherto been more as a protocol review group (evaluating externally produced protocols).

(ii) We also believe there are missed opportunities for imaging and translational work as part of the metastatic portfolio as the focus has been on drug therapeutic studies rather that these allied disciplines. We will address this issue as a cross-cutting theme.

(iii) We will continue to work with the Cancer Research Networks and companies to ensure good geographical distribution of trial sites. It is particularly important when one looks at segments of disease (such as those with BRCA mutations) where relatively few sites will open in the UK and we need to ensure that those sites are well distributed and that lines of communication are open between cancer centres and cancer units to ensure cross-referral of potentially eligible patients.

(iv) On a related note many of the studies currently opening are examining patients with rare mutations. This often requires some degree of pre-screening of archival or current tumour biopsies. An important part of strategy would be to explore the possibility of pre-screening at local sites to ensure the maximum number of patients are screened and identified as potentially eligible. By employing this strategy we hope to increase access to a wide number of studies to the maximum possible patient population and ensure equitable access to targeted clinical trials.

The Subgroup strategy can be seen overleaf.

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To horizon scan the portfolio to identify future gaps & to develop trial concepts for discussion within such areas To design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk Explore opportunities for identifying cross cutting themes across the portfolio & for coupling / decoupling studies where appropriate	All	Ongoing
1b. Portfolio development (local therapy)	Explore opportunities for evaluation of surgery / RT technology • new technologies in localised treatment radiotherapy/surgery	AR / MB AM	Ongoing
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to molecular classification To promote use of informative experimental models including focussing novel treatment evaluation to those Metastatic disease using plasma detectable ctDNA or metastatic disease accessible for biopsy To promote access to downstream trials based on identification of targets based on identified genomic alteration or target expression To identify key questions within existing conventional treatments where clinically meaningful post licence refinement Is amenable to exploration within clinical trial such as scheduling and combination	AR/NT/ PS/ RR All	

Strategic objective	Activity	CSG Lead	Date	Outcomes
1d Portfolio development integrated (translational research)	Promote expectations for integrating translational research into all trials where possible (patient acceptability / cost considerations) • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease Develop virtual Biobank (guided by Translational subgroup) • cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc.			
2 Collaborative approach to trial development & participation	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive studies • National Breast Trialists Day • Widespread Networking at Local and National International meetings • British Breast Group, NCRI National meeting , UKBCM Harnessing expertise and linking people with related ideas to maximise efficiency & quality to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (eg multiple biopsies) • Arrange forums for discussion • Ensure PPI representation at meetings • Aim to optimise efficiency in and minimise inconvenience to PPI representatives in relation to workload management Maximise opportunities for international collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All MM/KR DR/DC/JB		

Strategic objective	Activity	CSG Lead	Date	Outcomes
3b. Improving trials methodology & clinical utility	Endeavour to identify new targets amenable to optimisation within an academic/NHS setting Collaborate with Industry within Academic alliances and with individual companies for specific projects Engage with trials methodologists for optimising trial designs efficiently – multiple questions within nested trials. Ongoing evolution of trial design for uncommon subtypes utilising rare disease paradigms for efficacy evaluation	AR PS CP AR/JB/PS	Ongoing Ongoing	

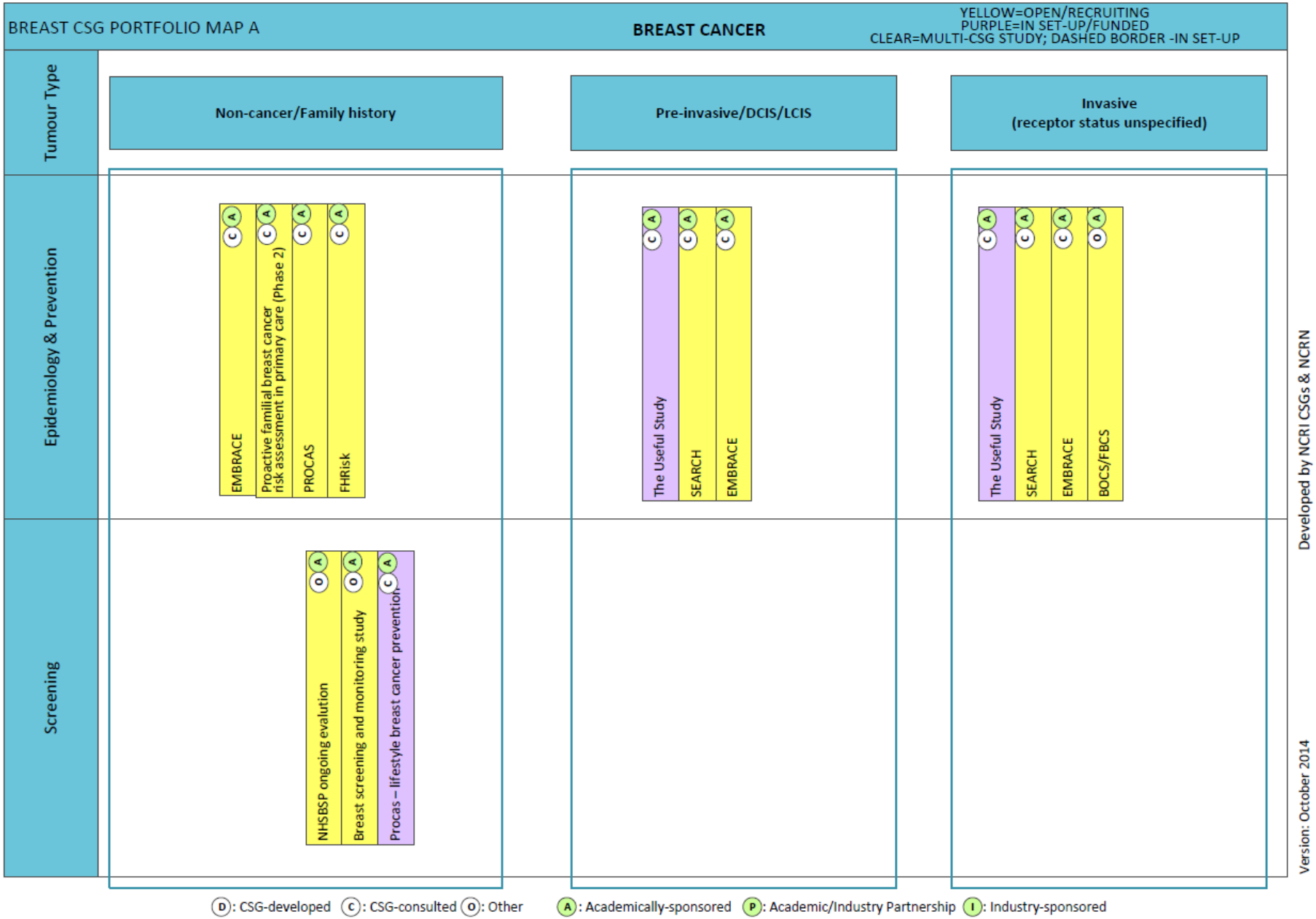
MB	Dr Mark Beresford
AH	Adrian Harnett
AM	Andreas Makris
DW	Duncan Wheatley
EB	Elizabeth Benns
MM	Mairead MacKenzie
KR	Kat Randle
AR	Alistair Ring
AA	Anne Armstrong
RC	Rob Colman
RR	Rebecca Roylance
PS	Peter Schmidt
NT	Nick Turner
CH	Catherine Harper Wynne

Appendix 3

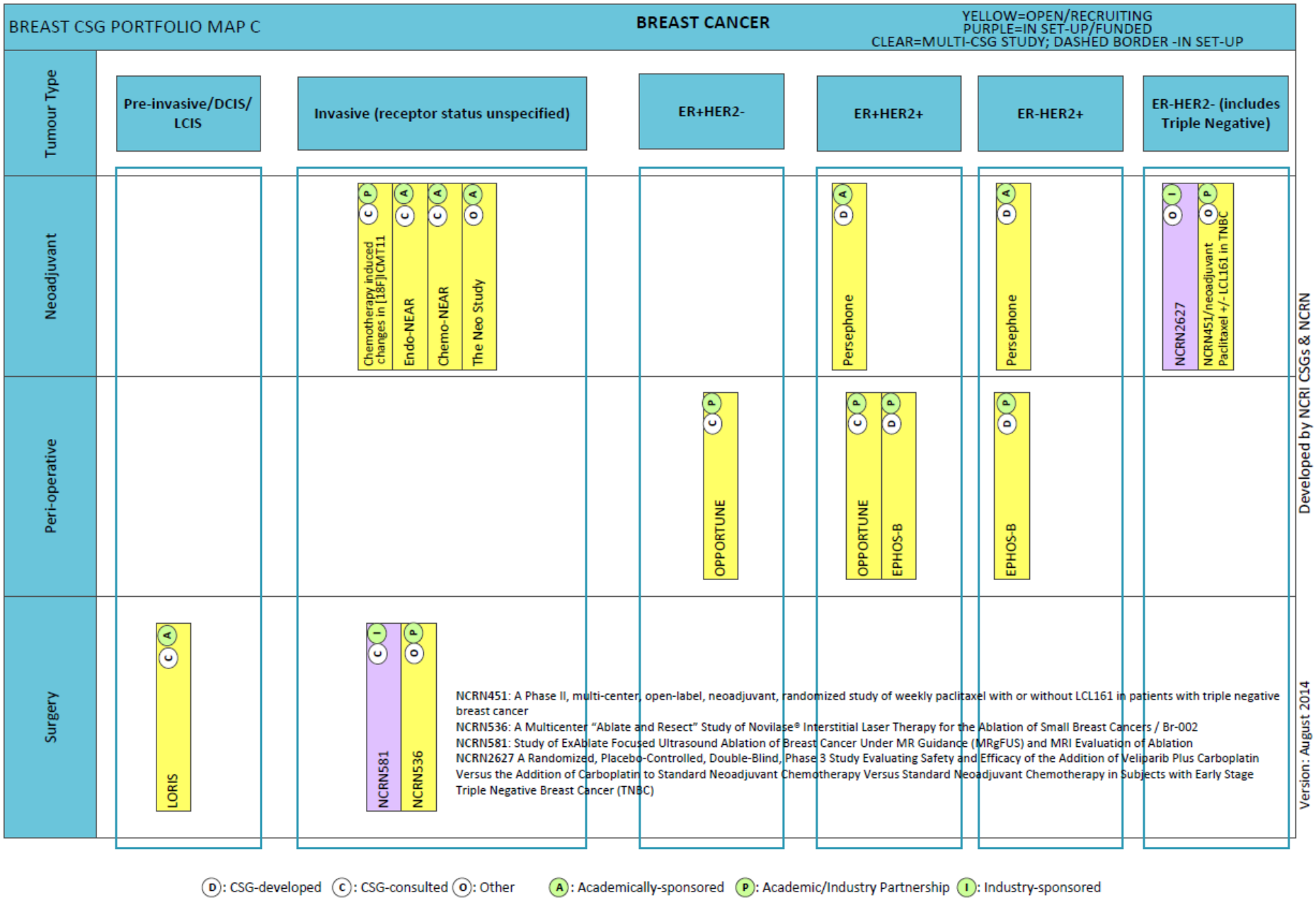
Portfolio maps

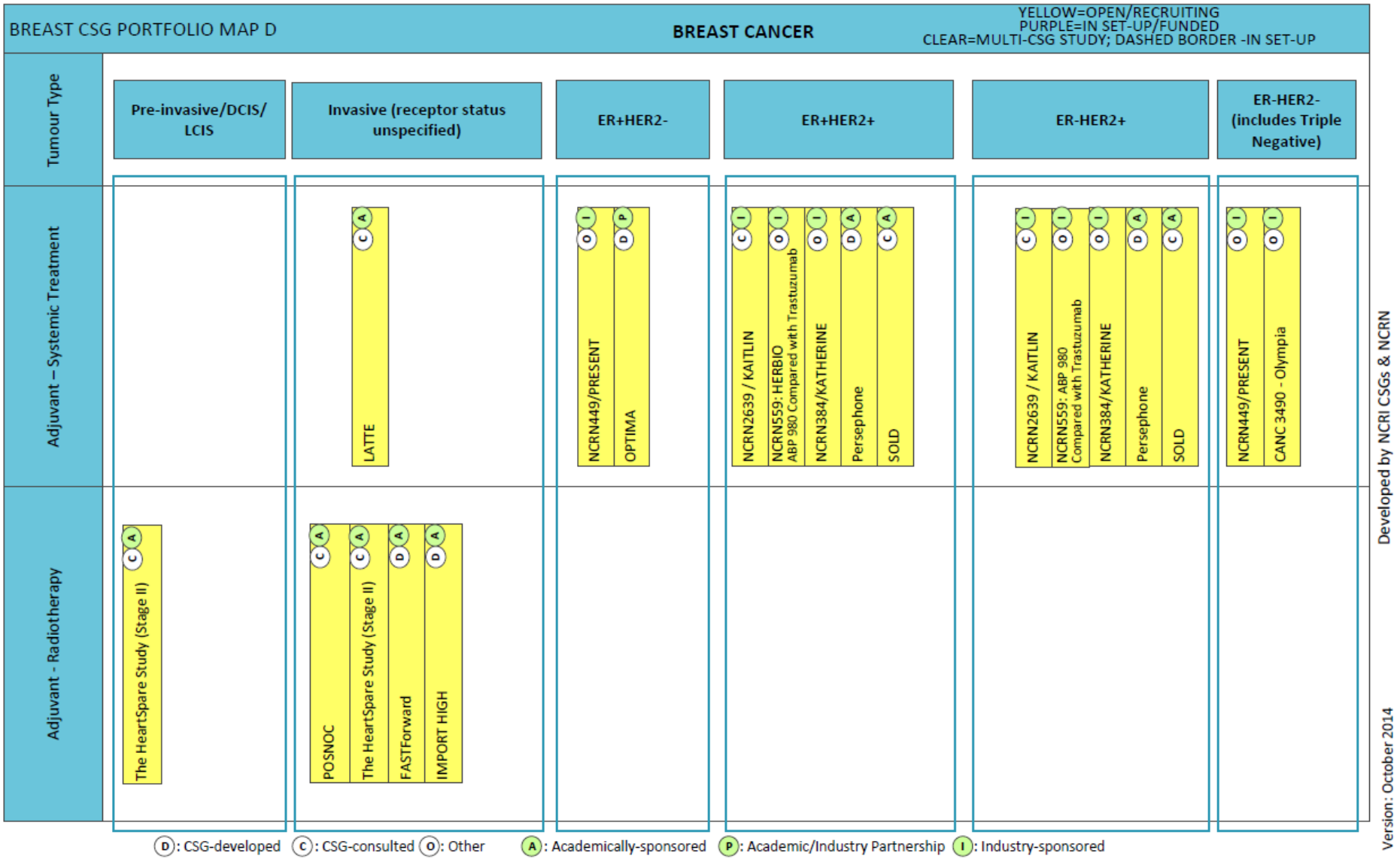
Breast Portfolio Map - Industry Studies Key

Acronym/Shortened Title	Full Title
NCRN189	PHASE 1/2, OPEN-LABEL, RANDOMIZED STUDY OF THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF LETROZOLE PLUS PD 0332991 (ORAL CDK 4/6 INHIBITOR) AND LETROZOLE SINGLE AGENT FOR THE FIRST-LINE TREATMENT OF ER POSITIVE, HER2 NEGATIVE ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN
NCRN327	AN OPEN-LABEL, RANDOMISED PHASE 1B/2 STUDY OF PF-04691502 IN COMBINATION WITH LETROZOLE COMPARED WITH LETROZOLE ALONE IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE, HER-2 NEGATIVE EARLY BREAST CANCER
NCRN565	Observational registry of Eribulin use in advanced BCEribulin (HALAVEN®) Use for the Treatment of Advanced Breast Cancer: A Prospective Observational Registry
NCRN378e	PARP Inhibitor - An Open-Label, Multicenter, Phase 2 Study of Poly(ADP-Ribose) Polymerase (PARP) Inhibitor E7449 in Combination with Carboplatin and Paclitaxel in Subjects with Advanced Breast Malignancies - PHASE II ARM 3 (cohort 4)
NCRN365	A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Breast Cancer or Other Solid Tumor
NCRN494	Exploratory open label study of GM-CSF coding oncolytic adenovirus CGTG-102, with low dose cyclophosphamide. Part I in patients with refractory injectable solid tumours; Part II in soft tissue sarcoma, breast cancer and melanoma
CANC-3548	: A phase Ib/II study of LEE011 in combination with fulvestrant and BYL719 or BKM120 in the treatment of postmenopausal women with hormone receptor positive, HER2 negative locally recurrent or advanced metastatic breast cancer (LEE011X2108)
NCRN617	RELATED Octreotide for diarrhoea prevention in mBC - A randomised, multicentre, open-label, 2- arm-controlled, Phase II study of prophylactic Octreotide aimed to prevent/reduce diarrhoea in metastatic breast cancer (MBC) patients treated with Lapatinib plus Capecitabine
NCRN581	Study of ExAblate Focused Ultrasound Ablation of Breast Cancer Under MR Guidance (MRgFUS) and MRI Evaluation of Ablation
NCRN-2627	A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects with Early Stage Triple Negative Breast Cancer (TNBC)


BREAST CSG PORTFOLIO MAP A
BREAST CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Non-cancer/Family history
Pre-invasive/DCIS/LCIS
Invasive
(receptor status unspecified)
Epidemiology & Prevention
EMBRACE
Proactive familial breast cancer risk assessment in primary care (Phase 2)
PROCAS
FHRisk
The Useful Study
SEARCH
EMBRACE
The Useful Study
SEARCH
EMBRACE
BOCS/FBCS
Screening
NHSBSP ongoing evalution
Breast screening and monitoring study
Procas – lifestyle breast cancer prevention
Developed by NCRI CSGs & NCRN
Version: October 2014
D: CSG-developed
C: CSG-consulted
O: Other
A: Academically-sponsored
P: Academic/Industry Partnership
I: Industry-sponsored

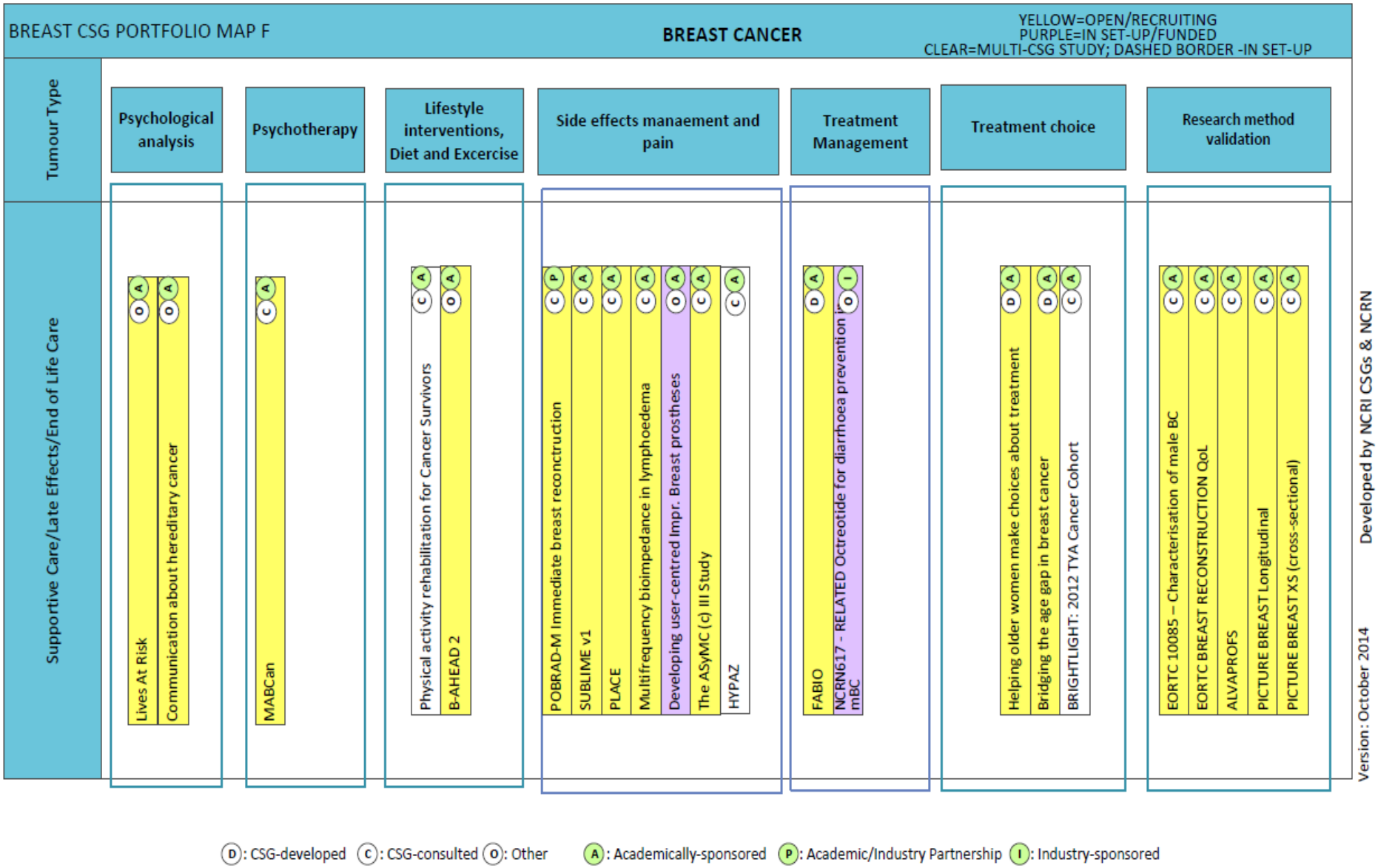
BREAST CSG PORTFOLIO MAP B
BREAST CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Diagnosis/Imaging
Non-cancer/Family history
Pre-invasive/DCIS/LCIS
Invasive (receptor status unspecified)
ER+ HER2-
ER+ HER2+
ER- HER2+
ER-HER2- (includes Triple Negative)
Digital breast tomosynthesis in younger symptomatic women
MAMMO-50
Clinical data collection for SPECIALS
Educational tool improve radiographers' decision making on when to perform repeat mammography views
EBLIS
GE tomosynthesis versus supplementary mammographic views
Digital breast tomosynthesis in younger symptomatic women
COPE
ICBP MODULE 4
CRUK STRATIFIED MEDICINE
MIMIC
FABB
FAB-IE
POPPET
Digital breast tomosynthesis in screening younger higher risk wo
Educational tool improve radiographers' decision making on when to perform repeat mammography views
MIMIC
Vacuum-assisted and conventional core biopsy of axillary lymph nodes
PET Study - effect of chemo on caspase 3/7 activation
MagSnoll
Multifrequency Bioimpedance in the Early Detection of Lymphoedema
CRUK STRATIFIED MEDICINE
Staging the axilla in breast cancer: PET/CT
PLACE
COPE
Digital breast tomosynthesis in younger symptomatic women
NCRN2517 - Cerenkov Luminescence Imaging in breast ca
TN-PET01
Developed by NCRI CSGs & NCRN
Version: October 2014
(D): CSG-developed (C): CSG-consulted (O): Other (A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

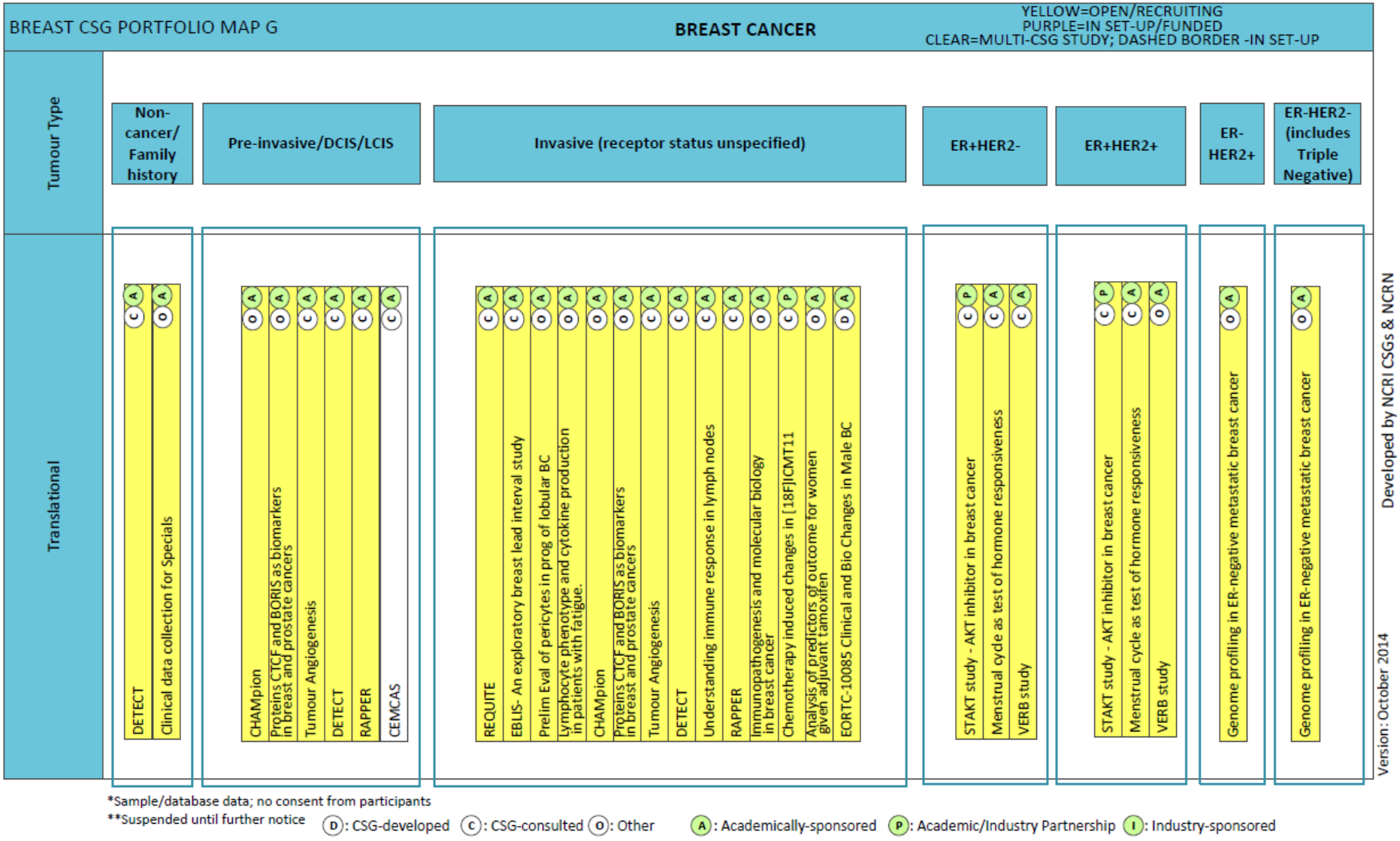

BREAST CSG PORTFOLIO MAP C
BREAST CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Pre-invasive/DCIS/ LCIS
Invasive (receptor status unspecified)
ER+HER2-
ER+HER2+
ER-HER2+
ER-HER2- (includes Triple Negative)
Neoadjuvant
Chemotherapy induced changes in [18F]ICMT11
Endo-NEAR
Chemo-NEAR
The Neo Study
Persephone
Persephone
NCRN2627
NCRN451/neoadjuvant Paclitaxel +/- LCL161 in TNBC
Peri-operative
OPPORTUNE
OPPORTUNE
EPHOS-B
EPHOS-B
Surgery
LORIS
NCRN581
NCRN536
NCRN451: A Phase II, multi-center, open-label, neoadjuvant, randomized study of weekly paclitaxel with or without LCL161 in patients with triple negative breast cancer
NCRN536: A Multicenter "Ablate and Resect" Study of Novilase® Interstitial Laser Therapy for the Ablation of Small Breast Cancers / Br-002
NCRN581: Study of ExAblate Focused Ultrasound Ablation of Breast Cancer Under MR Guidance (MRgFUS) and MRI Evaluation of Ablation
NCRN2627 A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects with Early Stage Triple Negative Breast Cancer (TNBC)
Developed by NCRI CSGs & NCRN
Version: August 2014
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored



NCRN449: Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax™ Treatment/PRESENT
NCRN559: A Randomized, Double-Blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared with Trastuzumab in Subjects with HER2 Positive Early Breast Cancer
NCRN2639 / KAITLIN: A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III TRIAL COMPARING TRASTUZUMAB PLUS PERTUZUMAB PLUS TAXANE FOLLOWING ANTHRACYCLINES VERSUS TRASTUZUMAB EMTANSINE PLUS PERTUZUMAB FOLLOWING ANTHRACYCLINES AS ADJUVANT THERAPY IN PATIENTS WITH OPERABLE HER2 POSITIVE PRIMARY BREAST CANCER

BREAST CSG PORTFOLIO MAP E
BREAST CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Metastatic – 1st line
Metastatic – 2nd line
Metastatic – 3rd line, etc
ER+
ER+ HER2+
HER2+
Triple Negative
BRCA
HER2-/Other
CANC-3548
NCRN2973
FAKTION
NCR2844 Enzalutamide in Combination with Exemestane
NCRN454/BELLE3
NCRN2678 FINESSE
AT13148
MANTA
NCRN550/BOLERO 6 - everolimus + exemestane vs everolimus vs capecitabine
NCRN565 – eribulin (obs)
RADICAL, v1.0
Abiraterone Acetate
NCRN548/BOLERO4
ARISTACAT – AI +/- saracatinib
NCRN186/ALTERNATIVE
NCRN559
NCRN565 – eribulin (obs)
AT13148
NCRN526 - Nala
NCRN628 / TNACITY
PAKT
NCRN378e PARP Inhibitor
AT13148
NCRN - 3216 BMN 673
NCRN2808
NCRN2888
NCRN2787 BravO
NCRN365 – oral rucaparib
AT13148
6MP & low-dose methotrexate - BRCA tumours
NCRN2802 -OLYMPIAD
CIPHER
AT13148
NCRN - 2787 BravO
NCRN396
NCRN407/BELLE4
FGFR study - Proof-of-concept study of AZD 4547
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored
Version: October 2014
Developed by NCRI CSGs & NCRN


BREAST CSG PORTFOLIO MAP F
BREAST CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Supportive Care/Late Effects/End of Life Care
Psychological analysis
Psychotherapy
Lifestyle interventions, Diet and Excercise
Side effects manaement and pain
Treatment Management
Treatment choice
Research method validation
Lives At Risk
Communication about hereditary cancer
MABCan
Physical activity rehabilitation for Cancer Survivors
B-AHEAD 2
POBRAD-M Immediate breast reconctruction
SUBLIME v1
PLACE
Multifrequency bioimpedance in lymphoedema
Developing user-centred Impr. Breast prostheses
The ASyMC (c) III Study
HYPAZ
FABIO
NCRN617 - RELATED Octreotide for diarrhoea prevention in mBC
Helping older women make choices about treatment
Bridging the age gap in breast cancer
BRIGHTLIGHT: 2012 TYA Cancer Cohort
EORTC 10085 – Characterisation of male BC
EORTC BREAST RECONSTRUCTION QoL
ALVAPROFS
PICTURE BREAST Longitudinal
PICTURE BREAST XS (cross-sectional)
Version : October 2014
Developed by NCRI CSGs & NCRN
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored



*Sample/database data; no consent from participants

**Suspended until further notice

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

Appendix 4

Publications in the reporting year

OPTIMA trial

Wason, J., A. Marshall, J. Dunn, R. C. Stein and N. Stallard (2014). Adaptive designs for clinical trials assessing biomarker-guided treatment strategies. *Br J Cancer* 110(8): 1950-1957.

POSH study

Maishman T, Copson E, Stanton L, Gerty S, Dicks E, Durcan L, Wishart GC, Pharoah P; POSH Steering Group, Eccles D. An evaluation of the prognostic model PREDICT using the POSH cohort of women aged ⩽40 years at breast cancer diagnosis. *Br J Cancer*. 2015 Mar 17;112(6):983-91. doi: 10.1038/bjc.2015.57.

Copson ER, Cutress RI, Maishman T, Eccles BK, Gerty S, Stanton L, Altman DG, Durcan L, Wong C, Simmonds PD, Jones L, Eccles DM; POSH Study Steering Group. Obesity and the outcome of young breast cancer patients in the UK: the POSH study. *Ann Oncol*. 2015 Jan;26(1):101-12. doi: 10.1093/annonc/mdu509. Epub 2014 Oct 30

IMPORT HIGH study

EM Donovan, C Brooks, RA Mitchell, M Mukesh, CE Coles, PM Evans, EJ Harris, on behalf of the IMPORT Trial Management Group. The Effect of Image Guidance Dose Distributions in Breast Boost Radiotherapy. *Clinical Oncology* Vol 26, issue 11, Nov 2014 671 - 676

E.M. Donovan, E.J Harris, M. Mukesh, J Haviland, J Titley, C Griffin, C.E. Coles, P.M. Evans on behalf of the IMPORT Trials Management Group. The IMPORT HIGH Image Guided Radiotherapy (IGRT) Study: A model for assessing IGRT *Clinical Oncology* vol 27, issue 1, Jan 2015, 3 - 5

EJ Harris, M Mukesh, R Jena, A Baker, H Bartelink, C Brooks, J Dean, EM Donovan, S Collette, S Eagle, JD Fenwick, PH Graham, JS Haviland, AM Kirby, H Mayles, RA Mitchell, R Perry, P Poortmans, A Poynter, G Shentall, J Titley, A Thompson, JR Yarnold, CE Coles, PM Evans, on behalf of the IMPORT Trials Management Group. Evaluation of Image Guided Radiotherapy for more accurate partial breast intensity modulated radiotherapy: comparison with standard imaging technique. *Efficacy and Mechanism Evaluation* 2014, Vol 1, issue 3

SOFT trial

Francis PA, Regan MM, Fleming GF, Lang I, Ciruelos E, Bellet M, Bonnefoi HR, Climent MA, Prada GA, Burstein HJ, Martino S, Davidson NE, Geyer CE, Jr., Walley BA, Coleman R, Kerbrat P, Buchholz S, Ingle JN, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Colleoni M, Viale G, Coates AS, Goldhirsch A, Gelber RD, the SOFT Investigators' Group and the International Breast Cancer Study Group (2014). Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 372(5):436-46

LORIS

A Francis, L Fallowfield, D Rea The LORIS Trial: Addressing Overtreatment of Ductal Carcinoma In Situ. *Clinical Oncology* 27 (1), 6-8 2014

L Fallowfield, L Matthews, A Francis, V Jenkins, D Rea Low grade Ductal Carcinoma in situ (DCIS): How best to describe it? *The Breast* 23 (5), 693-69 2014

TACT trial

Hall E, Cameron D, Waters R, Barrett-Lee P, Ellis P, Russell S, Bliss JM, Hopwood P (2014). Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing regimen and standard anthracycline based chemotherapy for early breast cancer: 6 year results from the UK TACT trial (CRUK/01/001). *Eur J Cancer* 50(14):2375-89.

Irshad S, Gillett C, Pinder SE, A'Hern R P, Dowsett M, Ellis IO, Bartlett JM, Bliss JM, Hanby A, Johnston S, Barrett-Lee P, Ellis P, Tutt A (2014). Assessment of microtubule-associated protein (MAP)-Tau expression as a predictive and prognostic marker in TACT; a trial assessing substitution of sequential docetaxel for FEC as adjuvant chemotherapy for early breast cancer. *Breast Cancer Res Treat* 144(2):331-41

TEAM trial

Sabine VS, Crozier C, Brookes CL, Drake C, Piper T, van de Velde CJH, Hasenburg A, Kieback DG, Markopoulos C, Dirix L, Seynaeve C, Rea DW**,** and Bartlett JMS. Mutational analysis of PI3K/AKT Signalling Pathway in Tamoxifen Exemestane Adjuvant Multinational (TEAM) pathology study. *JCO* 32 (27) 2951-295 2014

J Stephen, G Murray, DA Cameron, J Thomas, IH Kunkler, W Jack G.R. Kerr, T. Piper, C. L. Brookes, D. W. Rea, C. J. van de Velde, A. Hasenburg, C. Markopoulos, L. Dirix, C. Seynaeve, and J. M. Bartlett., Time dependence of biomarkers: non-proportional effects of immunohistochemical panels predicting relapse risk in early breast cancer *Br J Cancer* 111, no. 12 (2014): 2242-7

Engels CC, Charehbili A, van de Velde CJH, Bastiaannet E, Sajet A, Putter H, van Vliet EA, van Vlierberghe RLP, Smit VTHBM, Bartlett JMS, Seynaeve C, Liefers GJ, Kuppen PJK. The prognostic and predictive value of Tregs and tumor immune subtypes in postmenopausal, hormone receptor-positive breast cancer patients treated with adjuvant endocrine therapy: a Dutch TEAM study analysis. *Breast Cancer Res Treat* Feb 2015;149(3):587-96

MAPLE trial

Leary A, Evans A, Johnston SR, A'Hern R, Bliss JM, Sahoo R, Detre S, Haynes BP, Hills M, Harper-Wynne C, Bundred N, Coombes G, Smith I, Dowsett M (2015). Antiproliferative effect of lapatinib in HER2-Positive and HER2-Negative/HER3-high breast cancer: results of the presurgical randomized MAPLE Trial (CRUK E/06/039). *Clin Cancer Res* online 15 November 2014

NEOCENT trial

Palmieri C, Cleator S, KilburnLS, Kim SB, Ahn SH, Beresford M, Gong G, Mansi J, Mallon E, Reed S, Mousa K, Fallowfield L, Cheang M, Morden J, Page K, Guttery DS, Rghebi B, Primrose L, Shaw

JA, Thompson AM, Bliss JM, Coombes RC (2014). NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. *Breast Cancer Res Treat* 148(3):581-90.

QUEST trial

Winters ZE, Griffin C, Horne R, Bidad N, McCulloch P (2014). Barriers to accrue to clinical trials and possible solutions. *Br J Cancer* 111(4):637-9.

Winters ZE, Emson M, Griffin C, Mills J, Hopwood P, Bidad N, MacDonald L, Turton EP, Horne R, Bliss JM on behalf of the QUEST Trial Management Group (2015). Learning from the QUEST multicentre feasibility randomization trials in breast reconstruction after mastectomy. *Br J Surg* 102(1):45-56.

Others

Kilburn L, Banerji J, Bliss J, on behalf of the NCRI Breast Clinical Studies Group (2014). The challenges of long-term follow-up data collection in non-commercial, academically-led breast cancer clinical trials: the UK perspective. *Trials* 15:379.

Guidelines developed by subgroups

Pinder SE, Rakha E, Purdie CA, Bartlett JMS, Francis A, Stein RC, Thompson AM, Shaaban AM on behalf of the Translational Subgroup of the NCRI Breast Clinical Studies Group. Macroscopic handling and reporting of breast cancer specimens pre- and post-neoadjuvant chemotherapy treatment; review of pathological issues and suggested approaches. *Histopathology* (Epub ahead of print January 2015)

Rea D, Francis A, Hanby A, Spiers V, Rakha E, Shaaban A, Chan S, Vinnicombe S, Ellis I, Martin SG, Jones JL, and Berdichevski F. Inflammatory breast cancer: Time to standardise diagnosis assessment and management, and for the joining of forces to facilitate effective research. *British Journal of Cancer* 2015, in press

Appendix 5

Major international presentations in the reporting year

TACT 2

Bayani J, Morden J, Barret-Lee P, Canney P, Cameron D, Bliss J (2014). Androgen receptor expression is an independent marker of low residual risk in the TACT2 trial (CRUK/05/019). 2014 San Antonio Breast Cancer Symposium:#P4-11-03.

FAST-Forward

Brunt AM, Yarnold J, Wheatley D, Somaiah N, Kelly S, A H, Coles C, Goodman A, Zotova R, Sydenham M, Griffin C, Bliss J (2014). Acute skin toxicity reported in the FAST-Forward trial (HTA 09/01/47): a phase III randomised trial of 1-week whole breast radiotherapy compared to standard 3 weeks in patients with early breast cancer. NCRI National Cancer Conference; 2014; Liverpool:#LB116

IMPORT LOW

Coles CE, On behalf of the IMPORT Trial Management Group (2014). Partial breast radiotherapy for women with early breast cancer: First analysis of late cosmesis adverse events from IMPORT LOW (CRUK/06/003) NCRI National Cancer Conference; 2014; Liverpool:#B260

Partial breast radiotherapy for women with early breast cancer: first analysis of late cosmesis adverse events from IMPORT LOW (CRUK06/003). On behalf of the IMPORT Trial Management Group. Abstract number EBCC 0454; Oral presentation, EBCC-9, Glasgow, Scotland. 19 – 21 March 2014

ABC

Hiscox S, Smith C, Nicholson R, Gee J, Harris A, Bliss J, Kalaitzaki E, Sestak I, Dowsett M, Cuzick J, Ellis I, Barrett-Lee P (2014). Nuclear β-catenin negativity predicts for late relapse in ER+, tamoxifen-treated breast cancer. 2014 San Antonio Breast Cancer Symposium 2014:#P3-06-1.

TACT 2

Morden J, Bliss J, Bayani J, Canney P, Barrett-Lee P, Bartlett J, Cameron D (2014). Intrinsic subtypes and BCL2 as predictive marker of low residual risk in the TACT2 trial (CRUK/05/019). 2014 San Antonio Breast Cancer Symposium:# P4-11-04.

POETIC

Segal C, Gao Q, Gellert P, Li T, Miller C, Mardis E, Martin L, Holcombe C, Skene A, Bliss J, Robertson J, Smith I, Dowsett M, on behalf of the POETIC Trial Management Group (2014). Exome sequencing of post-menopausal ER+ breast cancer (BC) treated pre-surgically with aromatase inhibitors (AIs) in the POETIC trial (CRUK/07/015). 2014 San Antonio Breast Cancer Symposium:#S1-04

Qiong Gao, Pascal Gellert, Tiandao Li,Christopher A Miller, Elaine Mardis, Lesley-Ann Martin,Roger A'Hern, Chris Holcombe, Anthony Skene, Judith Bliss, John Robertson, Ian Smith, Mitch Dowsett,

POETIC Trial Management Group and Trialists, Exome sequencing of post-menopausal ER+ breast cancer (BC) treated pre-surgically with aromatase inhibitors (AIs) in the POETIC trial (CRUK/07/015). San Antonio 2014

TNT trial

Tutt A, Ellis P, Kilburn L, Gillett C, Pinder S, Abraham J, Barret S, Barrett-Lee PJ, Chan S, Cheang M, Fox L, Smith I, Thompson R, Tovey H, Wardley A, Wilson G, Harries M, BLISS J (2014). The TNT trial: A randomised phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). 2014 San Antonio Breast Cancer Symposium:#S3-01

OPPORTUNE study

Schmid P, Pinder SE, Wheatley D, Macaskill J, Zammit C, Hu J, Price R, Bundred N, Hadad S, Shia A, Lim L, Sarker S-J, Gazinska P, Woodman N, Korbie D, Trau M, Mainwaring P, Parker P, Purushotham A, Thompson AM. Preoperative window of opportunity study of the PI3K inhibitor pictilisib (GDC-0941) plus anastrozole vs anastrozole alone in patients with ER+, HER2-negative operable breast cancer (OPPORTUNE study). San Antonio Breast Cancer Conference 2014. S2-03

ARTEMIS

ARTemis: A randomised trial of bevacizumab with neoadjuvant chemotherapy (NACT) for patients with HER2-negative early breast cancer—Primary endpoint, pathological complete response (pCR) Helena Margaret Earl, Louise Hiller, Clare Blenkinsop, Louise Grybowicz, Anne-Laure Vallier, Jean Abraham, Jeremy Thomas, Elena Provenzano, Luke Hughes-Davies, Karen McAdam, Steve Chan, Rizvana Ahmad, Tamas Hickish, Stephen Houston, Daniel Rea, John M. S. Bartlett, Carlos Caldas, David A. Cameron, Janet Dunn, Richard L Hayward, for ARTemis Investigators; J Clin Oncol 32:5s, 2014 (suppl; abstr 1014)

Earl H, Hiller L, Dunn J, Blenkinsop C, Grybowicz L, Vallier A-L, Abraham J, Thomas J, Provenzano E, Gounaris I, Hughes-Davies L, McAdam K, Chan S, Ahmad R, Hickish T, Houston S, Rea D, Bartlett J, Caldas C, Cameron D, Hayward L. ARTemis: A randomised trial of bevacizumab with neo-adjuvant chemotherapy for patients with HER2-negative early breast cancer: primary endpoint - pathological complete response. 10th NCRI (National Cancer Research Institute) Cancer Conference (Liverpool, UK, November 2-5, 2014)

Appendix 6

Strengths & weaknesses from the 2014 Progress Review

Strengths

- A clear, well written report
- A very strong group with a well developed and functioning subgroup structur
- Very good leadership at both group and subgroup level
- Sustained high levels of recruitment over a number of years
- High success rate at funding committees, with the exception of BEMERP, and in delivering internationally practice changing trials
- The Group is particularly congratulated on its window platform as it is unlikely that these studies could be done outside the UK
- Strong international reputations within the Group, but this may not be the same for the Group *per se*
- The publication rate in high impact journals and number of presentations at key international meetings are to be commended
- Excellent relationships with CTAAC, who particularly value their well organised and comprehensive comments on trial submissions, which are viewed as exemplary
- A clear process for considering BIG trials in the UK, which is working well
- An inclusive Group and is justifiably proud of the way in which consumers and younger researchers are supported and included in the Group's activities
- Consumer involvement is particularly strong (the Panel was impressed with the setting up of a consumer led working party on symptom management)
- A highly effective relationship with the ICR CTSU and Professor Bliss is congratulated on the support that she, as CTU Director, and her team provide
- Annual trials meetings are well attended and highly valued by the research community
- The Group has addressed the vast majority of issues from the last review.

Issues for the CSG to consider

- It is not clear whether the Group has the same international visibility and reputation as its individual members, and this needs to be addressed
- The CSG needs to develop a clear 3-5-year research strategy for the main group and for the subgroups, which will need review and possible updating on an annual basis
- The Group should influence what research comes forward, rather than being purely reactive
- Clear reference is needed as to what studies might be of highest priority for the window platform trials
- The CSG should reflect on whether the hub and spoke mechanisms proposed for the metastatic disease setting could be applied to other parts of the Group's portfolio as a management tool for trials that are difficult to recruit to
- Question whether there are opportunities to be gained by the CSG developing high level SOPs and a standard framework for specimen and data-sharing between trials and banks, in order to maximise the research opportunities - it should be possible to develop a prospective

framework that would make sense to major charities and sponsors and which they could accept going forward

- Work needs to be done to clarify for external and international audiences, including younger researchers, how things work organisationally in the UK
- The Panel felt the CSG had missed a couple of opportunities to work with SWOG by not collaborating on two initiatives which fell outside the remit of IRCI and encouraged the Group to seek international collaboration where necessary and possible
- Explore, with the breast cancer charities possibilities, for funding patient travel and/or admin support for the Group
- Look for ways to improve or systemise its interactions with the Biomarker and Imaging CSG
- Consider setting up mini circles of consumers to share out the heavy potential workload
- Continue the increase in recruitment to trials

Issues for the NCRI/CRUK to consider

- Pathology costs to be raised at high levels within NCRI and CRUK