NCRI
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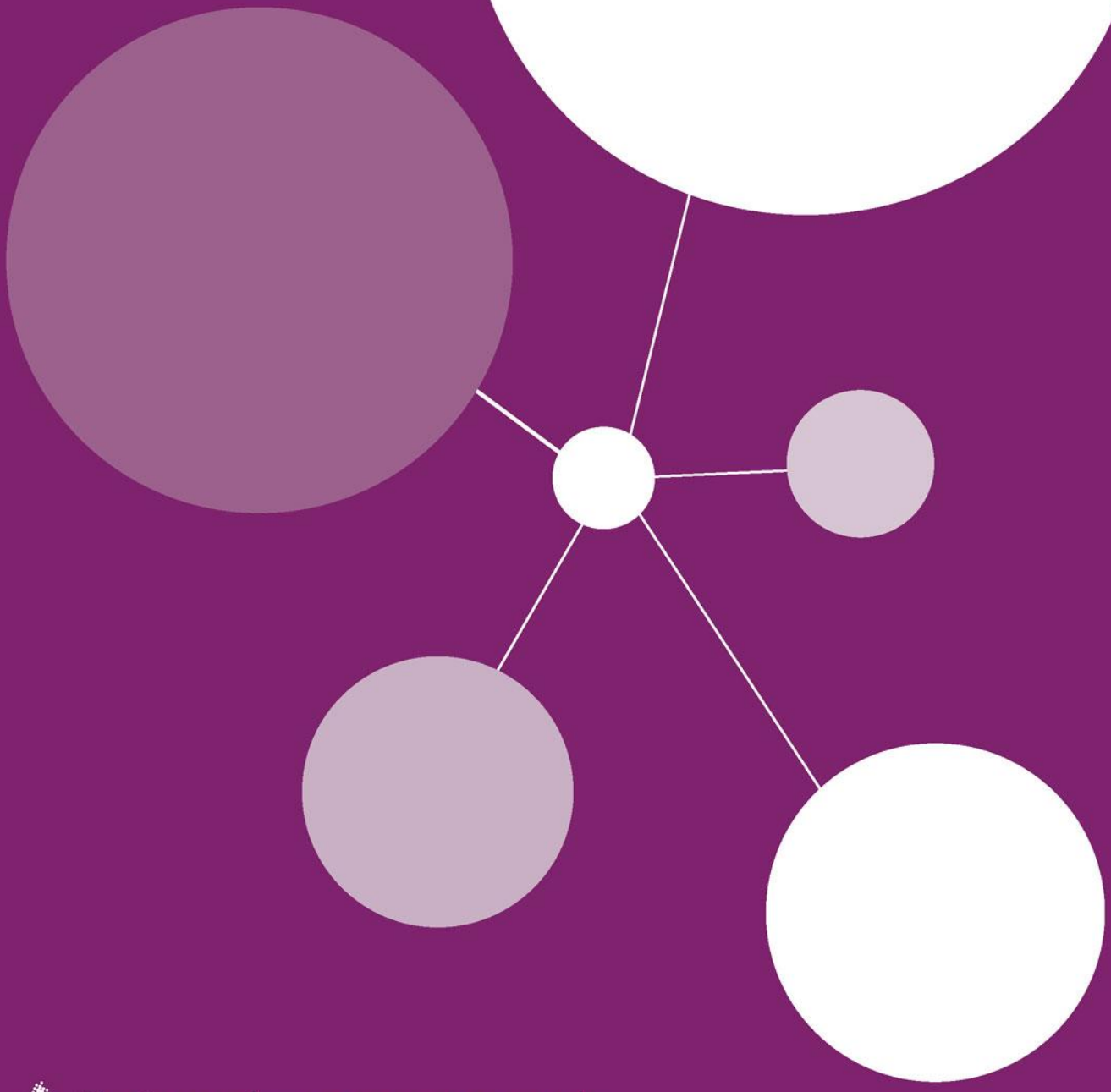
NCRI Bladder Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Bladder Cancer CSG Annual Report 2014/15

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

Bladder cancer is the seventh most common cancer in the UK but the fourth most common cancer in UK men with 10,399 new cases diagnosed in 2012 and 5242 deaths over the same period. There is a male to female preponderance with 7452 new male diagnoses (72%) and 2941 (28%) female giving a male to female ratio of 2.5:1. An average of 53% were diagnosed in the age group 75 years or older, and 9 in 10 aged 60 or over, which given an increasingly ageing UK population emphasises the importance of developing new treatments and reducing treatment related toxicity in this tumour site. Survival in bladder cancer lies starkly behind that of many other cancers. Despite the number of incident cases falling by 19% over a ten year period between 1999 and 2009, (10,742 in 1999 to 2009 in 2009)[1] the overall number of deaths fell by only 10%, (4546 in 1999 to 4132 in 2009), indicating that survival is actually worsening (Eylert MF et al).[2]

Bladder cancer research funding appears substantially lower than for other site specific tumours. (1.3 % of 2013 total site specific NIHR partners).

The top achievements for the CSG are:

- Successful CSG Progress Review report and maintenance of the mantra "A trial for every patient"
- Successful completion of trials in systemic therapy, TOUCAN (cisplatin unfit), PLUTO (second line chemotherapy) with publication of the SUCCINCT Trial data
- Succession planning for systemic therapy with opening of new studies in neoadjuvant and second line setting, and ongoing recruitment to portfolio and funding of new studies.
- Ongoing promotion of the Bladder portfolio and engagement with the wider uro-oncological community via close links with BAUS, BAUS Oncology, British Uro Oncology Group, BAUS Section of Academic Oncology and BAUN. Trial managers for the studies in portfolio have promoted the portfolio at national meetings of these organisations.

The key challenges for the CSG have been:

- Developing a process with which to engage with the newly appointed urology subspeciality leads in the NIHR.

- Continuing to develop academic studies/ partnership studies in the face of unprecedented interest from Industry and potential competing studies in crowded arena of second line chemotherapy.
- Developing strategy for working with the research priorities identified by the 2015 publication of the NICE Bladder Cancer Management Guidance, to ensure the foci of priority identified by the CSG and its national audit of NCRN Networks of barriers to recruitment are not lost.
- Ensure protocols in NMIBC are permissive with commonality of endpoints.

References:
1.Cancer Research UK Key Facts Bladder Cancer. http://www.cancerresearchuk.org/cancer-info/cancerstats/keyfacts/bladder-cancer/uk-bladder-cancer-statistics
2.Falling bladder cancer incidence from 1990 to 2009 is not producing universal mortality improvements. Journal of Clinical Urology July 4 2013. Http://iro/sagepub.content/early/2013/07/03/20151415813492724.full.pdf.

2. Structure of the Group

The Main CSG Consists of 17 members, five clinical oncologists, five urological surgeons, three medical oncologists, two consumer members, one pathologist and one statistician. Membership is drawn from across the UK. Bladder cancer remains a niche area of both treatment and research active clinicians and several members of the Group have been re-appointed, an acknowledgement of the difficulty in replacing their expertise. An aggressive programme of subgroup re-structuring and new membership and a policy of mentorship of new investigators via the subgroups and working parties has been adopted. Applicants who are unsuccessful in application to the main CSG due to lack of direct experience as Chief Investigator are encouraged to undergo mentoring and become co-applicants on studies in development through the subgroup and working party structure. In addition, the Bladder CSG has appointed in Nov 2014 two Trainees for a one year appointment to promote their personal development as the future investigators. Funding for one of these posts is from the British Uro Oncology Group, demonstrating the close working with other organisations.

The CSG has two subgroups: the T2 and Below Sub group (TABS) and the Advanced Bladder Cancer Subgroup. The T2 and below Subgroup is Chaired by Miss Jo Cresswell and the Advanced Bladder cancer Subgroup by Professor John Chester until May 2014, when Dr Simon Crabb was appointed Chair. Professor Chester had been instrumental to successful delivery of the Advanced Subgroup portfolio and having been present since its inception, stepped down from both the subgroup and the main Bladder CSG by virtue of change in specialist interest.

The Penile Cancer Subgroup membership and Chair have been reviewed with Professor Amit Bahl appointed as subgroup Chair in 2013.

The T2 and below subgroup membership includes surgical and non surgical oncologists with the aim of fostering speciality collaboration. The former Chair of the BAUS Section of Oncology Mr Tim O'Brien has been an invited member and a full list can be seen in Appendix 3.

Radiation and chemo-radiation studies are linked to both subgroups. The neo-adjuvant working party Chaired by Professor Tom Powles is linked primarily with the T2 and Below Subgroup. In Jan 2015 both subgroups met on the same day to allow membership engagement across groups Subgroups hold a minimum of two teleconferences and one face to face meeting per annum.

3. CSG & Subgroup strategies

Main CSG

The Bladder CSG is outlined in Appendix 2A. A Strategy Day is planned for October 2015 to develop wider uro-oncology community key research priorities.

Penile Subgroup (Chair, Dr Amit Bahl)

In the last year the Penile Subgroup has supported two clinical trials addressing chemotherapy options in 1st line metastatic penile cancer (VinCaP) and 2nd line metastatic penile cancer (JAVA-P). Both these trials are recruiting as estimated in the trial timelines.

The main strategy for the Penile Subgroup is the implementation of the InPACT trial which is a multinational trial addressing several issues in the management of penile cancer. The aim is to open the trial in the UK on 1st October 2015 with the trial opening in the US not long after and subsequently the Scandinavian countries. This trial is integral to the strategy of the Subgroup as it addresses international collaboration and formalisation of radiology, pathology, surgery, chemotherapy and radiotherapy in this rare cancer.

Future strategy will be to focus on translational studies once the trial set-up and recruitment is established and collaboration for studies such as HPV related cancers and novel treatment strategies are under initial discussion.

Strategies to increase recruitment of the current trials with the Penile Subgroup promoting awareness of these at several national forums like BAUS, BAUN and also the BUG newsletter.

The Penile Subgroup has supported the national dataset histopathology reports publication and Dr Cathy Corbishley (core member of the Subgroup) has been asked to be the international lead on the WHO pathology guidelines

Despite the challenge of dealing with a rare cancer and the risk of recruitment failure in clinical trials, the Subgroup has through a unified focus and international collaboration tried to overcome this obstacle.

Consumer representation remains a challenge and approach to charities working in this field is being done to enable consumer representation.

Advanced Cancer Subgroup (Chair, Dr Simon Crabb)

In the last year the Advanced Disease Subgroup has overseen progress towards successful completion of CSG developed trials. The primary report for SUCCINCT is now published. Recruitment was completed to LaMB (accepted for oral presentation at ASCO 2015), TOUCAN and PLUTO. NeoBLADE, FIESTA and ToTem are recruiting in a satisfactory manner.

The aims of the Subgroup are firstly to develop novel targeted therapeutic options in advanced disease, linked to known or putative predictive biomarkers, for transfer ultimately to evaluation in the neoadjuvant/radical setting. A second linked aim is to address the recommendation from this year's Progress Review panel report that we strengthen our translational research interests.

The main challenges to the Subgroup remain recruitment rates in this disease setting and the emergence of multiple commercial studies over the last year (which is almost unprecedented for bladder cancer).

With these aims and challenges in mind the Subgroup's proposed strategy for future development of the CSG portfolio is to consolidate efforts around the ATLANTIS trial which was approved this year by CTAAC. This study will test novel targeted maintenance therapies following first line chemotherapy with biomarker stratification for treatment arms. This will build on the significant success of the LaMB trial in terms of delivery of a stratified approach to clinical evaluation of promising targeted agents in this disease. The SPIRE trial has also recently been approved for funding through the Combinations Alliance/NAC. The Subgroup is developing a translational research program based around these and other recent portfolio studies.

T2 & Below (TABS) Subgroup (Chair, Miss Jo Cresswell)

The Subgroup membership has changed to improve representation including appointing a consumer representative (Mr Andrew Winterbottom) and trainee (Dr Rachel Pearson) as core members. The Subgroup also mentors future members of the main CSG. The group facilitates engagement between surgical and non-surgical oncologists, as well as scientists, statisticians and other members of the multi-disciplinary team. Investigators are encouraged to present their ideas at an early stage to benefit from the experience of the team. The main achievements have been in supporting the development of 4 trials, which are currently recruiting (CALIBER, POUT, PHOTO, HYBRID). Also a further trial has been funded and is due to open shortly (RAIDER). Two now closed studies are due for publication this year (BOXIT and HYMN). The Subgroup offers a forum for collaborative working between specialties which particularly lends itself to trials requiring support from the MDT e.g. surgical support for RAIDER. Future strategy is to develop studies in quality of life and survivorship, as well as novel treatments for NMIBC. Challenges include the potential for overcrowding of the NMIBC portfolio with multiple trial ideas in this area. This may be addressed in part by utilising multi-arm trial design.

4. Task groups/Working parties

First established three years ago, the neo-adjuvant working party is chaired by Professor Tom Powles. Whilst the working party has maintained its ambition to develop a biomarker driven neoadjuvant study, derived from work on tissue bio-bank and from data on the metastatic population in LamB trial, it was agreed that an interim study was required for this patient group. The NeoBlade study is investigator led by Dr Syed Hussein and with industry support, adding the targeted agent nintedanib to standard gemcitabine-cisplatin chemotherapy and is currently recruiting. The MIRTOS study has been funded (March 2015) and is a window study in patients due to undergo radical cystectomy but for whom neo-adjuvant chemotherapy is not appropriate, and is an international collaboration.

If current studies using check point inhibitors in advanced disease prove positive, the UK will be well placed to deliver such agents in a study in the neoadjuvant setting.

The recent Progress Review panel report made the suggestion that we strengthen our translational research interests. In response to this, the CSG is currently bringing together a working party to undertake this role.

5. Patient recruitment summary for last 5 years

CSG development is defined as actively developed from within the Group or by a member of the main CSG or one of the Sub Groups with CSG endorsement and is commented on with the trial description.

There have been three studies close in systemic therapy with successors planned or already funded. The rate of recruitment to RCT remains unchanged, and the opening of new trials in MIBC and NMIBC which together hope to recruit 1000+ patients aims to improve this.

In the Bladder CSG portfolio, 5 trials closed to recruitment and 7 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	274	342	274	342	2.7	3.4
2011/2012	63	340	63	340	0.6	3.4

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	0	324	0	324	0.0	3.1
2013/2014	648	287	648	287	6.2	2.7
2014/2015	69	262	69	262	0.7	2.5

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

Both the European Uro Oncology Group and the RTOG have brought specific studies to the CSG seeking collaboration. At present these studies were unsuitable for current UK implementation, or had barriers for trial sponsorship. However, this has opened dialogue to allow early discussion to enable input into protocols from UK investigators to maximise joint protocols and endpoints. The MIRTOS study, a window study prior to cystectomy is a collaborative study with European collaborators.

The penile InPACT Study has been developed in collaboration with the EORTC and the US under the auspices of the International Rare Cancers Initiative (IRCI).

POUT has been presented at both the EAU and at the European Uro-Oncology Group meetings and European sites have demonstrated interest in the study- site opening has been hampered by funding in local countries despite the strong levels of interest in the study. Both the German Cancer Group and Denmark have expressed strong interest but been unable to secure funding.

The portfolio maps have been shared with the ANZUP Australia and New Zealand Uro Oncology Group to facilitate discussion.

There is representation on the Molecular Biomarkers Advisory Group from Professor Tom Powles who is also EORTC liaison. Dr Robert Huddart is the designated link with CTRad.

At the national workshop on PDT strategies and implementation the Bladder CSG was strongly represented on this, having a portfolio study (PHOTO) open using this technology.

The Psychosocial Oncology & Survivorship (POS) CSG were represented at a Bladder CSG meeting and members of the POS CSG are currently working on two studies for funding submission: QoL after radical treatment in MIBC (CI Dr Ashok Nikapota)and the proposed biomarker directed selection of radical treatment study BIOPIC (CI Prof Robert Huddart). Work is ongoing both with the Imaging Advisory Group and a number of trials currently in portfolio (IDEAL: open RAIDER: funded, MARBLE: currently single centre early chemotherapy response) have imaging components. Funding applications are planned for use of DW-MRI to correlate MRI response to neo-adjuvant chemotherapy with subsequent pathological specimen. An imaging sub-study of retrospective review of CT Urograms in planned for the POUT Trial. The POUT trial of adjuvant chemotherapy versus surveillance in completely resected upper tract TCC translational sub-study (POUT-T) aims to identify urinary, serum and tissue biomarkers over expressed or down-regulated by treatment to obtain a predictive nomogram to better inform diagnostic staging prior to nephroureterectomy.

Liaison with the British Association of Urological Surgeons (BAUS) Section of Oncology, the Action on Bladder Cancer, the British Uro Oncology Group remains robust. Bladder CSG members sit on each of these Committees and collaboration has been demonstrated with the national audits on barriers to recruitment and advanced bladder cancer circulated nationally as a joint venture.

CSG members (Dr Birtle, and prior to his rotation off the CSG, Mr Catto) work closely with the International Patient Awareness and Support Group, Fight Bladder Cancer (FBC)/Bladder Cancer UK. Studies are publicised through these organisations and Dr Birtle is working with Fight Bladder cancer to set up Patient Research Champions based on geography. In addition Mr Andrew Winterbottom, Chair FBC, is the newly appointed lay member of the CSG and attends both subgroups, and is patient representative on a number of studies either open or in development.

Newsletters and emails go out to the 15 sub-speciality leads after each CSG meeting and Subspeciality leads have been tasked with specific issues to discuss regarding upcoming trials e.g. biomarker directed treatment MIBC with their network urologists to get real time input into trials at feasibility stage.

A strategy afternoon is planned for the October 2015 CSG meeting and the speciality leads will be invited to this. 4/15 leads are already Bladder CSG members.

7. Funding applications in last year

There has been success in translational, biomarker and radiotherapy studies building on successful applications documented in last year's Annual Report in NMIBC which are currently in set up phase or recently opened to recruitment.

Via the BAUS Annual Scientific meeting and Section of Academic Urology, it has been possible to publicise studies at an early stage in funding submission and to gain both recognition and interest from the uro oncology community. This allows potential barriers to recruitment to be identified. Trials in development have been publicised at the British Uro Oncology Meetings, BAUN and BAUS, and this theme of Trials Under Construction (i.e. those funded but not yet open) will be highlighted at the Joint Renal/Bladder CSG Road Shows to be held in May 2015 in Birmingham.

The tables below summarise applications related to the Group in the last year.

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
JAVA-P second line chemotherapy in advanced/metastatic penile cancer.	Full application Endorsement of Investigator Lead industry Study	Prof Amit Bahl	Endorsed.
November 2014			
ATLANTIS - Maintaining response in urothelial cancer: A personalised precision medicine trial	Full application	Professor Thomas Powles/Dr Robert Jones	Funded
March 2015			
VIPER: Vitamin D in the immuno-prevention of early recurrence of bladder cancer.	Outline application	Dr Kieran Jefferson	Not funded
MIRTOS: A phase II study investigating preoperative MPDL3280A prior to surgery in operable transitional cell carcinoma of the bladder.	Full application *Endorsement*	Professor Tom Powles	Funded
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
SPIRE- Phase I /IIa clinical trial combining SGI-110 (DNA Methyltransferase inhibitor) with gemcitabine/cisplatin chemotherapy in patients with advanced solid tumours including bladder tumours	CR-UK New Agents Committee/ Combinations Alliance (Astex Pharmaceutical)	Dr Simon Crabb/ Mr James Catto	Funded
Image directed Bladder Pathway Redesign study	HTA CET Outline Submission	Professor Nick James	Pending
BRAVO - High grade bladder cancer; a randomised controlled trial of radical cystectomy agaimnst intravesical immunotherapy- a feasibility study	Yorkshire Cancer Research	Mr James Catto	Funded
A study of patient reported outcomes after diagnosis of bladder cancer	Yorkshire Cancer Research	Mr James Catto	Funded

8. Collaborative partnership studies with industry

There is currently one open CSG consulted/led and industry sponsored study in portfolio (ROCHE- second/third line metastatic bladder cancer) of MPDL3280 versus chemotherapy.

The two other studies listed are either across all CSG (NCRN 396) or adopted onto portfolio without CSG involvement (NCRN 517). The CSG has been instrumental in the Pharma Alliance Initiative particularly with AZ and this has meant emphasis on Collaborative studies and investigator led sponsored studies rather than industry sponsored at present.

The Bladder CSG were initial members of the AZ Initiative and have continued to lead in this area with partnerships on new technologies such as Hyperthermia and on systemic studies of fist line, second line, platinum unfit and maintenance therapy.

There are currently eight partnership studies with industry in portfolio. A recent NCRN CSG portfolio analysis of recruiting studies in the period Feb-March 2014 showed that the majority of bladder interventional trials were partnership rather than pure academic.

Examples of newly funded studies in alliance or industry:

- The Spire study is a Combinations Alliance trial that involves partnership between Southampton and Sheffield ECMCs, Astex Pharmaceuticals and CR-UK (NAC)
- The ATLANTIS trial was successfully funded this year by CTAAC and is now in development. This currently includes partnership with two pharmaceutical companies.
- MIRTOS is a window study in collaboration with Roche investigating pre-operative MPDL 3280A prior to surgery in operable TCC of the bladder and in collaboration with 4 EU Countries.

9. Impact of CSG activities

The CSG impact over the last five years on routine clinical practice has been substantial.

Routine clinical practice has been transformed, based on data from three portfolio studies. At least one of the approaches listed below has become standard treatment in all UK and many European Centres, giving centres robust data on which to make informed treatment decisions.

The international impact of the portfolio UK delivered phase III randomised BC2001 study of chemo radiation versus radiation alone in MIBC cannot be underestimated, with a field shift akin to that of concurrent chemoradiation for cervical cancer. This is the largest trial to have been conducted addressing how best to optimise radiotherapy in patients with MIBC. This has changed practice and made bladder preservation standard of care in appropriate patients.

The BC2001 study has challenged the established dogma of surgical treatment being gold standard and this has significantly widened the treatment choice for patients

The Phase III BCON protocol of concurrent hypoxia modification with carbogen and nicotinamide has become standard practice in some UK areas. The optimum schedule combining BCON and BC2001 protocols remains undefined and thus centres have adopted one rather than both of these protocols.

The Phase II GEMEX study of concurrent radiosensitisation chemotherapy has also been adopted in some centres.

ODMIT C, a single installation of mitomycin C after nephrouretectomy reducing the risk of subsequent bladder cancer is an established component of international guidelines.

The TPF study, the first combination chemotherapy multi-centre study in advanced penile cancer has been published, although this was a negative study it demonstrated the ability of delivering such studies in a niche patient group by ensuring collaboration across all penile supra-network team clinicians nationally.

The International Collaboration of Trialists Advanced Bladder Cancer (ABC) Working Party published its long-term results of phase III trials of neo-adjuvant chemotherapy in patients with MIBC treated by cystectomy or radiotherapy. The ABC meta-analysis reported a significant survival advantage after 10 years from 30 to 36% equating to a 16% relative reduction in the risk of death and establishing neo-adjuvant therapy as a standard of care for patients with MIBC.

Recruitment for SUCCINCT, an early phase gemcitabine/cisplatin plus triplet study, was noted to have been challenging and behind initial predictions which should be considered for future proposals in this setting. The result was essentially negative, with no evidence of improved efficacy when combining sunitinib with cisplatin/gemcitabine, but with a clear increase in toxicity (mostly myelosuppression). The study report was published as a breaking news item in European Urology in December 2014, together with an Editorial on gemcitabine/cisplatin plus therapy by the CSG Chair.

The CSG has been extensively involved in workshops on new tech such as PDT and in each new agents call by Industry partners.

The CSG has provided robust feedback on the consultation document from the National Institute for Clinical Excellence on Bladder Cancer Guidance.

Four members of the CSG were in addition members of the NICE Guidelines Development Group

CSG members provide input into Macmillan Information sheets on bladder cancer.

CSG members are also on the NICE guidance implementation group and have commented as stakeholders on all requests involving bladder cancer such as review of screening, review of GP referrals and diagnosis pathway and on the current NICE Bladder Cancer Quality Standards.

The CSG comments on applications coming to CTAAC whether developed within or outside of the CSG and to NIHR via the Industry adoption route .This allows early feedback to Industry partners as to whether a study may be deliverable in the UK by virtue of patient population or clinical interest at an early stage .

Funding submissions to HTA or RfPB may be brought to the CSG for evaluation and it is usual for CI to bring studies to the CSG to ask for review and comment prior to submission and for letter of support from the CSG Chair.

10. Consumer involvement

The CSG has two consumer members who are involved throughout the pathway of studies from inception to implementation. There is full participation from lay members in feedback from the CSG for CTAAC and the HTA. The consumer members are vital in ensuring that pragmatic trials are considered, minimising loss of potential recruitment after study opening.

Mrs Jean Gallagher

I am now entering my final year of membership of the Bladder CSG as a lay member. I have a mentor in the group and have found other members who will also answer any questions I may have and have asked for comments on various issues. My comments are encouraged throughout and between meetings.

I am now a co-applicant of a study with other members of the group.

I have attended and contributed to the NCRI Conference in Liverpool and the Bladder and Renal Roadshow in Birmingham.

The increased knowledge, understanding and confidence I have gained within this group have allowed me to develop. I am now a co-applicant in two funded end of life studies and I have helped form and co-chair a Service User and Carer Research Group in the Faculty of Health at Bradford University, which is now providing support to PHD students and other NHS research.

The continuing support of the chair has been invaluable.

Mr Andrew WInterbottom

I joined the Bladder Cancer CSG at the end of 2014 as a consumer member. My first meetings were attendances to the Advanced Bladder Cancer and the TABS Subgroups in January this year.

Although it is still early days, I have found that the medical and research members have been very helpful with initial guidance and being positive about hearing opinions from a lay member.

I am now involved with 4 specific trials myself at various stages from initial scoping through to the final stages. I will also shortly be a speaker at the Renal and Bladder Cancer Trials Roadshow in Birmingham.

One part of the role of a consumer member of a CSG is to be able to bring forward ideas and suggestions for the betterment of the work of the CSG. To this end I have attended training courses run by the NCRI and taken part in group meetings with consumer members of other CSGs across a spectrum of different cancers. A close network is currently being developed with consumer members of the other urological CSG's in order that we can be as proactive as possible.

As founder and director of the Fight Bladder Cancer charity we have now started looking at setting up a team of regional patient representatives to assist in trial recruitment and retention. Through our national support forum we have recently run "virtual" sessions with members to help on two specific trials.

I am looking forward to continue working towards being an active participant across all the activities of the Bladder CSG and its subgroups.

The continuing support of the other members of the CSG and the chair has been invaluable.

11. Open meetings/annual trials days/strategy days

The CSG holds a bi-annual trials meeting jointly with the other urological CSGs and as such, the next such event is planned for Jan 27 2016. Previous feedback from 2014 meeting was excellent and published in 2014 CSG report.

There is a regional road-show jointly with the Renal CSG planned for May 10 2015 during which the portfolio will be highlighted, barriers to recruitment individually, locally, regionally and nationally discussed, and research priorities discussed. Funding for this and arrangements have been achieved by the CSG Chairs (Renal and Bladder).

A first meeting with the NIHR Subspeciality leads was challenging as the lead for urology is required to meet with four separate CSGs (Bladder/Renal/Prostate/Testis) and as such minimal impact could be made for any Group via such an event. All Subspeciality leads are invited to the upcoming strategy session in Oct 2015.

Specific trials such as POUT hold bi-monthly teleconferences for PI/CNS/Research nurses involved in the POUT trial to ensure sharing of best practice. The TOP TIPS for Recruitment have been re-written with specific information for urologists and oncologists recruiting into the study, using evidence from the qualitative sub-study.

There have also been three Regional recruitment strategy meetings for the POUT trial held in 2014, in Bristol, Birmingham and London. A further virtual meeting is planned for Scottish Centres in Jan 2015

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

Areas identified at the 2011 progress review and Annual Report from 2012, 2013, 2014 have been targeted. The 2015 progress review comments have been incorporated into the CSG strategy as the Review took place shortly before submission of Annual Report.

Changing and improving pattern of recruitment and barriers to research, improving profile of bladder trials across networks

Areas identified from CSG barriers to recruitment questionnaire have looked at those that we can address from the CSG namely pragmatic studies (7.1%), deliverable in the smaller units (8.9%) and better publicity of trials through the MDT. The current portfolio balances complex IMP studies with those in NMIBC that can be easily implemented in smaller units with little additional clinician/research nurse time (CALIBER). Together with PHOTO, these two studies aim to deliver 700+ patients into NMIBC trials and maintain the engaged network of urologists.

The portfolio is publicised through the RSM Update Meetings, BAUS, BAUS Oncology/BAUS Section of Academic Oncology, BUG and BAUN.

The CSG members have been mapped onto each of the new CRN and individual members who are not the local urology sub-speciality leads tasked with promoting the portfolio with their local CRN and Division One Clinical Leads to ensure parity given to bladder studies.

Joint Road Show with the Renal CSG scheduled for May 2015.

Improving Recruitment to open studies

The trials of systemic therapy TOUCAN and PLUTO have recruited. PLUTO was closed 7 patients short of its original target after IDMC review concluded that it would not meet its primary endpoint. Prior to this the study was recruiting to both time and target. The FIESTA and TOTEM studies are due to complete in current year with recruitment target as planned. The POUT trial is recruiting to time and target. Its model of regional recruitment road-shows and regular teleconferences, together with "top tips" for recruiters based on qualitative work has provided a model for new studies in development.

There is proactive management of all portfolio studies with review of RAG reports and early discussion between CSG and TMG if recruitment levels are slower than anticipated to look at potential barriers.

The screening logs have been identified as vital tools to identify barriers to recruitment especially in areas of clinical equipoise. On example of this is in the POUT study where perception of chemotherapy has been identified as in need of modification and also clinicians' subconscious exclusion of older patients who were biologically fit for an adjuvant trial.

International colleagues collaboration and co-ordination

This remains a work in progress with ongoing discussions with the EORTC, the European Uro Oncology Group and the wider community. Currently MIRTOS has been funded in collaboration with investigators across Europe, the penile cancer InPACT trial as an international collaboration through the Rare Cancers Initiative and three members of the CSG (Prof Bahl, Dr Choudhary, Dr Birtle) are working with colleagues in Canada on a mutual study for post cysectomy adjuvant radiotherapy. Preliminary work on a joint study is to be presented at 2015 ASTRO meeting as oral presentation.

The Portfolio Maps are shared with the ANZUP GU Group to allow potential Expressions of interest.

Biobank resource and pathology committee

There is collaboration between BCON and BC2001 data banks to examine prognostic and predictive biomarkers to inform biomarker directed study in MIBC. (BIOPIC)

Work is continuing using the neo-adjuvant chemotherapy tissue bank on identification of biomarkers.

The recent Progress Review identified this as the key area to develop and this is a priority for 2015 year.

Greater collaboration with industry possibly on equipment studies

The CSG has been instrumental in the Pharma Alliance Initiative, particularly with AZ, with whom the CSG were initial members of the AZ initiative. There are partnerships on new technologies such as hyperthermia and on systemic studies of first line, second line, platinum unfit and maintenance therapy.

In 2013/2014 there were eight partnership studies with industry in portfolio. Work from the NCRI CSG portfolio analysis of recruiting studies in 2014 in the period Feb –March 2014 showed that the majority of bladder interventional studies were partnership rather than pure academic.

For 2015, ATLANTIS a precision medicine biomarker driven study in collaboration with Exelexis and Novartis has been funded in CTAAC Nov 2014 round and further discussions with Industry on Electromotive delivery devices studies (TEMPO) and hyperthermia are in development

Succession planning

Succession planning is evident, of both studies in pipeline and also of CSG membership. A mentoring structure has been initiated, as there is a current "dedicated pool" of bladder cancer research innovators. It is acknowledged there is a need to bring in enthusiastic clinicians who perhaps have less experience of being CI and to nurture through subgroups, providing mentorship and encouraging roles as co-applicants on studies. This has been currently demonstrated via the neo-adjuvant working party and advanced bladder cancer subgroup mentoring of a new Chief Investigator on a now funded portfolio study (NeoBlade)

The Bladder CSG has two new Trainee appointments, as part of the NCRN strategy, one of whom will link closely with the British Uro Oncology Group and thus ensure that the work of the CSG is widely publicised through the Trainee community of fledgling researchers .The CSG has a separate subgroup mentoring strategy of applicants initially unsuccessful to main CSG appointment, subsequently invited to join a subgroup and have been mentored in funding applications as CI or co-applicant. This will provide robust training for full CSG membership and research submission skills.

A clear pipeline is in place for NMIBC and MIBC- previous attempts at RCT of cystectomy versus radiation in MIBC have failed to recruit and the group has concentrated on radiation technique studies with adaptive planning and IGRT/IMRT funded (HYBRID/RAIDER)

Publications

As reflected in Appendix 4 more publications linked to portfolio have been captured.

Areas for consideration from annual report 2013/2014:

Reducing membership of penile subgroup

Increasing consumer representation in subgroups

Increasing recruitment to intervention trial

Appointing radiologists to the group

Work in progress to address feedback from 2013/2014

After discussion with Chair of penile subgroup, it has been agreed that the membership number is appropriate as the studies in this patient group require a united approach from all UK Supra-network centres in penile cancer and these are represented on the Subgroup. Numbers additional to those recommended do not receive expenses and subgroup meetings are held at a geographical site convenient for members to minimise expense or occur via teleconference.

Consumer representation to subgroups has occurred with the additional Lay member appointment to main CSG of Andrew WInterbottom (Also Chair of Consumer and Support Group Fight Bladder Cancer). This has allowed additional representation on subgroups without too much undue pressure on lay members. Further additional representation would be welcomed; bringing in for example members of the bladder trials consumer groups from the CTU's but is tempered by the overall numbers allowed to be appointed to a subgroup and provision of expenses from the NIHR.

Increasing recruitment to interventional studies remains ongoing and is a strategy aim for 2015 previously identified. The joint road shows with the renal CSG were designed to augment this.

Appointment of a radiologist to the Group is hoped to be achieved as part of the Spring 2015 CSG appointment round and informal discussions with interested parties is in progress.

13. Priorities and challenges for the forthcoming year

The Overall Group Strategy is to:

1. Improve quality of life and minimise treatment related side effects for patients with NMIBC

2. Improve cancer specific survival for patients with advanced disease.

For this strategy to be realised, our challenges and priorities overlap and are as outlined below:

The five year external review of the CSG held in February 2015 has outlined a number of areas for the CSG to take forward. A strategy session and SWOT analysis is planned to coincide with the Autumn CSG meeting and to define the top research priorities. This will need to be compared with the research priorities in the recently published NICE Bladder cancer Management guidance.

A meeting of the Advanced Sub-Group is planned for July 2015 with the direct aim of identifying members, (potentially bringing in international expertise) to use the collected tissue for biomarker and translational resource.)

Liaison with subspeciality leads has began and must be utilised to promote the "coming to a hospital near you" concept- the early sharing of information on funded studies likely to open within 6 months to allow Sub speciality leads to liaise with local Trusts, R and D and their CRN to ensure priority and promotion of these studies with appropriate allocation of resource. The leads will be encouraged to come to the CSG with barriers to recruitment and to opening studies in portfolio. Whilst the Sub-speciality leads are a valuable resource, their work is not restricted to bladder and as each sub-speciality lead must liaise with the other three urological CSG's (unlike the other tumour site specific speciality leads) there is likely to be a limit to the amount that can be asked of them.

Liaison with Fight Bladder Cancer as the leading patient led voice for Bladder Cancer has become more formalised and this gives the CSG the ability to develop patient research champions and map onto geographical areas by working with FBC.

Factors affecting recruitment and key challenges in 2015 recruitment

The national audit of networks has emphasised the main barriers to recruitment of clinician and research nurse time, studies that are deliverable in the cancer units and ones that have

significant patient numbers. PHOTO and CALIBER (533 and 174 patients respectively) aim to deliver 700 patients with NMIBC into interventional studies and the RAIDER study 240 patients with MIBC receiving radical radiotherapy

NMIBC Supporting recruitment to the currently funded studies CALIBER and PHOTO. It is essential to look for ways of fostering recruitment to more than one trial in the same patient group where the potential patient pool is substantial, so that further studies in NMIBC are not stifled during PHOTO recruitment process. This requires willingness to collaborate between CI on studies and permissive protocols.

MIBC It has proved thus far impossible to secure a united protocol for a successor trial to BC2001. Pragmatically therefore two studies of radiation technique, HYBRID and RAIDER, using hypofractionated radiation and IMRT respectively, and both with adaptive planning, image guided radiotherapy have been the subject of successful funding applications. These studies will engage the wider radiation oncology community by implementing state of the art radiotherapeutic techniques in a research setting.

It is vital to facilitate **collaboration** between surgical and non surgical disciplines to develop trials in MIBC. The previous portfolio study of selective bladder preservation versus cystectomy (The Spare Trial) has demonstrated the need for clinical equipoise and that this can impede recruitment and acceptance of randomised treatment. Where there is perceived to be a difficult randomisation e.g. the POUT trial of adjuvant chemotherapy versus surveillance in upper tract TCC, or with the newly developed BRAVO study of cysetctomy versus BCG in high risk NMIBC, a qualitative sub-study is embedded into the main study to allow real time feedback to clinicians to better inform consultation.

Advanced bladder cancer, the key challenge is that of competing studies in a niche area The interest of and engagement with Pharma has been very positive in bladder cancer but has led to a crowded market in for example, second line metastatic bladder cancer, an area where the group delivered strongly in the PLUTO trial. There are currently at least four proposed industry studies in this space and the CSG view is that with limited patient numbers , the development of academic studies in competition would be fruitless. The CSG have chosen to concentrate on implementation of and subsequent delivery into ATLANTIS, the CSG flagship study in first line metastatic bladder cancer. The future of this study is also tempered by Industry submissions in direct competition; whilst the CSG delivered strongly into the LAMB study and screening levels were significantly above target, there is little doubt that a competitor study would hamper recruitment.

In addition there is difficulty for studies in advanced disease of formally identifying the potential patient pool. Studies in this area have required close monitoring of recruitment rate seen with both SUCCINCT and TOUCAN, with modifications made including areas of the protocol, sample size and Patient information sheets. The CSG attempted to better quantify the number of patients with advanced bladder cancer are discussed per month in Uro-oncology MDT's, determining how many of those discussed saw an oncologist, how many were platinum fit. This audit despite contacting all uro oncology leads, research network managers and conducting through the British Uro-Oncology Group met with very a poor response rate- only five MDT's responded. This was perhaps a reflection of questionnaire fatigue and current pressures of busy clinical practice. The limited data available suggested that an average of 5 patients with

advanced urothelial cancer were discussed per month on a local MDT with approximately 3 being platinum fit.

14. Concluding remarks

It should be noted that our aims in the CSG to design and deliver research in bladder cancer may be affected by the NICE Guidance in Bladder Cancer published Feb 2015.

Review of the report shows that areas for research have been recommended to the extent of offering titles for specific research projects. This may have an unfortunate effect of stifling research brought to the CSG in other areas. The funding bodies who are NIHR partners and also NHS England and Commissioning Groups will potentially not support research other than that stated by NICE.

This is however an exciting time in bladder cancer with greater than ever interest from Industry. We must balance commercial studies with academic and partnership trials to maximise recruitment and patient choice.

Our aim for NMIBC remains to improve quality of life for patients by minimisation of treatment side effects, frequency of investigations, less invasive investigations and health economics studies to reduce resource overspend.

Personalised medicine is our goal for MIBC: building on the LamB trial successful screening to a biomarker directed study the ATLANTIS trial will continue to lead this strategy.

The changes in the NIHR Research Networks presents opportunities with identification of key members responsible as tumour site specific champions. However, the main barriers to recruitment identified in the CSG conducted national audit has identified research nurse capacity and clinician time as the main barriers. We have listened to the wish for pragmatic studies and submitted new studies in NMIBC for funding. The success of these studies relies on maintaining urologists engagement and trying to open new research sites with urologists as local PI's on these studies.

I cannot better my comment from last year's report about our key objective. I therefore state once more to reaffirm our commitment:

"Finally we must continue to embed patients at the heart of our research activity, from conception to implementation and working with other organisations to deliver studies that are attractive to Industry, clinicians, funders, and most importantly to our patients."

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

- A – Main CSG Strategy
- B – Penile Subgroup Strategy
- C – Advanced Cancer Subgroup Strategy
- D – T2 & Below (TABS) 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 Bladder Cancer CSG 2015 Progress Review

Dr Alison Birtle (Bladder Cancer CSG Chair)

Appendix 1

Membership of the Bladder Cancer CSG

Name	Specialism	Location
Dr Amit Bahl	Clinical Oncologist	Bristol
Dr Alison Birtle (Chair)	Clinical Oncologist	Preston
Dr Ananya Choudhury	Clinical Oncologist	Manchester
Dr Robert Huddart	Clinical Oncologist	London
Professor Nick James	Clinical Oncologist	Warwick
Dr Yvonne Rimmer	Clinical Oncologist	West Suffolk
Dr Rachel Pearson*	Clinical Research Associate	Newcastle
Dr Sebastian Trainor*	Clinical Research Fellow	Leeds
Mrs Jean Gallagher	Consumer	Bradford
Mr Andrew Winterbottom	Consumer	High Wycombe
Dr Simon Crabb	Medical Oncologist	Southampton
Dr Robert Jones	Medical Oncologist	Glasgow
Professor Thomas Powles	Medical Oncologist	London
Dr Emma Hall	Statistician	London
Miss Jo Cresswell	Surgeon	Middlesbrough
Mr Jeremy Crew	Surgeon	Oxford
Mr Mark Johnson	Surgeon	Newcastle
Mr Hugh Mostafid	Surgeon	Basingstoke
Mr Asif Muneer	Surgeon	London
Mr Param Mariappan	Surgeon	Edinburgh

* denotes trainee

Membership of the Subgroups

Advanced Cancer Subgroup		
Name	**Specialism**	**Location**
Dr Tony Elliot	Clinical Oncologist	Manchester
Dr Robert Huddart	Clinical Oncologist	London
Dr Maria Vilarino-Varela	Clinical Oncologist	London
Dr Sebastian Trainor*	Clinical Research Fellow	Leeds
Mr Andrew Winterbottom	Consumer	High Wycombe
Dr Simon Crabb (Chair)	Medical Oncologist	Southampton
Professor John Chester	Medical Oncologist	Cardiff
Dr Syed Hussain	Medical Oncologist	Liverpool
Dr Rob Jones	Medical Oncologist	Glasgow
Dr Steve Nicholson	Medical Oncologist	Leicester
Professor Tom Powles	Medical Oncologist	London
Professor Maggie Knowles**	Pathologist	Leeds
Mr Gareth Griffiths	Statistician	Southampton

T2 & Below (TABS) Subgroup		
Name	**Specialism**	**Location**
Dr Rob Huddart	Clinical Oncologist	London
Dr Ashok Nikapota	Clinical Oncologist	Brighton
Mr Andrew Winterbottom	Consumer	High Wycombe
Dr Rob Jones	Medical Oncologist	Glasgow
Dr Rik Bryan	Senior Research Fellow	Birmingham
Dr Emma Hall	Statistician	London
Ms Jo Cresswell (Chair)	Surgeon	Middlesbrough
Mr Mark Johnson	Surgeon	Newcastle
Mr Hugh Mostafid	Surgeon	Basingstoke

Penile Subgroup		
Name	**Specialism**	**Location**
Dr Amit Bahl (Chair)	Clinical Oncologist	Bristol
Dr Jim Barber	Clinical Oncologist	Cardiff
Dr Tony Elliot	Clinical Oncologist	Manchester
Dr Vincent Khoo	Clinical Oncologist	London
Dr Anita Mitra	Clinical Oncologist	London
Dr Cathy Corbishley	Histopathologist	London
Dr Steve Nicholson	Medical Oncologist	Leicester
Ms Clare Cruickshank	Statistician	London
Dr Emma Hall	Statistician	London
Mr Suks Minhas	Surgeon	London
Mr Asif Muneer	Surgeon	London
Mr Vijay Sangar	Surgeon	Manchester
Mr Nick Watkin	Surgeon	London

*denotes trainee

** denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The overall group strategy is to:

1. Improve quality of life and minimise treatment related side effects for patients with NMIBC
2. Improve cancer specific survival for patients with advanced disease.

The CSG will achieve this by:

a) Increasing and maintaining successful collaboration with industry on drug and device studies.

b) Ensuring that studies in NMIBC have inclusive protocols to maximise recruitment without compromise of trial integrity and continue to engage with the dedicated network of research active urologists.

c) Including biomarkers and imaging in trials and to develop a new working party to draw up translational strategy for the Group.

d) Drawing together data on chemo-sensitivity, platinum resistance and radiation sensitivity to inform further studies of personalised medicine.

e) Delivering large scale first line metastatic trial. Atlantis has now been funded and the CSG is fully behind delivery of the study once open. The design of the study makes it feasible to continue beyond the current planned agents and this study is central to CSG strategy.

f) Building on the success of the LaMB study the Bladder CSG has brought precision medicine to the forefront of its portfolio with check point inhibition studies in the pre cysetctomy window setting and in metastatic disease. Can we move these agents into other settings such as neo-adjuvantly or in NMIBC?

g) Enhancing recruitment with planned road-shows with Renal CSG encouraging smaller units and research naïve clinicians, especially urologists in busy district general hospitals to deliver pragmatic trials in NMIBC. This will need close liaison with the new NIHR Subspeciality Urology Leads.

h) Developing studies in end of life and symptom control in collaboration with Palliative & Supportive Care CSG.

i) Delivering robust studies evaluating quality of life after treatment for patients with both NMIBC and MIBC

B – Penile Subgroup Strategy

The overall Penile Subgroup strategy is to:

Improve cancer specific survival for patients with penile cancer and improve the evidence base for management of this rare cancer with trials with international collaboration.

The Penile Subgroup will achieve this by:

a) Increasing and maintaining successful international collaboration and formalisation of radiology, pathology, surgery, chemotherapy and radiotherapy in this rare cancer.

b) Ensuring that studies in Penile Cancer have robust protocols to maximise recruitment and continuing to engage with the dedicated network of research active urologists and oncologists.

c) Focus on translational studies once the international collaboration with the InPACT trial has been set-up and recruitment is established. Collaboration for subsequent studies such as HPV related cancers and novel treatment strategies are under initial discussion.

d) Enhancing recruitment with awareness of the current trials at several national forums like BAUS, BAUN and also the BUG newsletter.

e) Ensure Consumer representation with approach to charities working in this field to enable user feedback into trials in development and also for strategizing future work

C – Advanced Cancer Subgroup Strategy

In the last year the Advanced Disease Subgroup has overseen progress towards successful completion of CSG developed trials and transition to new CSG developed portfolio studies. The SUCCINCT (addition of sunitinib to first line chemotherapy in metastatic disease) has now been concluded and the primary report is now published. Recruitment was completed to LaMB (maintenance lapatinib in HER2/EGFR positive disease follow first line chemotherapy), TOUCAN (vandetinib in cisplatin ineligible patients) and PLUTO (second line pazopanib). Data from LaMB has been accepted for oral presentation at ASCO 2015 and represents the first stratified phase III trial in this disease. Data from TOUCAN and PLUTO will be presented in the next year. FIESTA and ToTem are recruiting in a satisfactory manner and anticipated to complete in the next year. In addition the CSG is supporting the investigator led trial NeoBLADE (nintedanib combined with neoadjuvant chemotherapy) which has opened to recruitment in 2014.

The key aims of the subgroup going forward are firstly to continue to look to develop novel targeted therapeutic options in advanced disease but with a greater emphasis on linking this to known or putative predictive biomarkers such that we can develop the basis for stratified medicine in this disease which remains an aspiration in routine practice. The successful completion of the LaMB trial demonstrates that we are leading the community in this regard and can deliver on stratified trials. We propose to develop these approaches in the advanced disease setting for transfer subsequently to evaluation in the neoadjuvant/radical setting. A second critical and linked aim is to address the recommendation from this year's Progress Review Panel Report that we strengthen our translational research interests. Indeed the subgroup had recently identified this as a need and agrees with the Panel's view that we are well placed to develop our activity in this area based around recent and planned translational sample sets from portfolio studies. An example of our potential here is the successful application for ATLANTIS (see below) that was predicated in part on translational data from the LaMB sample set.

The main challenges to the subgroup are twofold. Firstly, recruitment rates in this disease have been challenging historically. Recent years have seen portfolio studies that have recruited behind target (although each is now completed). Significant work has been undertaken through the CSG to address this and has seen some benefit in completion of studies, increase rates, wider PI engagement and probably also realism about what can be sensibly achieved. Secondly, we have seen the emergence of multiple large phase III commercial studies over the last year. These are mainly either for checkpoint inhibitor immunotherapies or FGFR targeted agents. This commercial interest is almost unprecedented for bladder cancer and is a change that the CSG portfolio will need to take account of in future development of its portfolio.

With these aims and challenges in mind the subgroup's proposed strategy for its contribution to the future development of the CSG portfolio is as follows. Firstly we will consolidate efforts around the ATLANTIS trial which was approved for funding this year by CTAAC. This study will test novel targeted maintenance therapies following first line chemotherapy with use of biomarker stratification for allocation to randomised treatment arms (each arm randomising experimental agent to placebo). It incorporates an adaptive design with the intention to add subsequent arms with future agents/biomarkers. This will build on the significant success of the LaMB trial in terms of delivery of an academic UK wide study to test a stratified approach to clinical evaluation of promising targeted agents in this disease. Development of successful arms (each with an initial phase II endpoint) would be intended to include rapid transfer to the radical setting as either neoadjuvant or adjuvant therapy. By focussing the advanced disease portfolio on ATLANTIS we believe that we can optimise recruitment

to optimise UK academic clinical research efforts in a manner that takes us towards development of a personalise medicine approach to bladder cancer. In addition, the subgroup is developing a translational research program based around ATLANTIS and other recent portfolio studies. The SPIRE trial has also recently been approved for funding through the Combinations Alliance/NAC to develop a DNA methyltransferase inhibitor/chemotherapy combination.

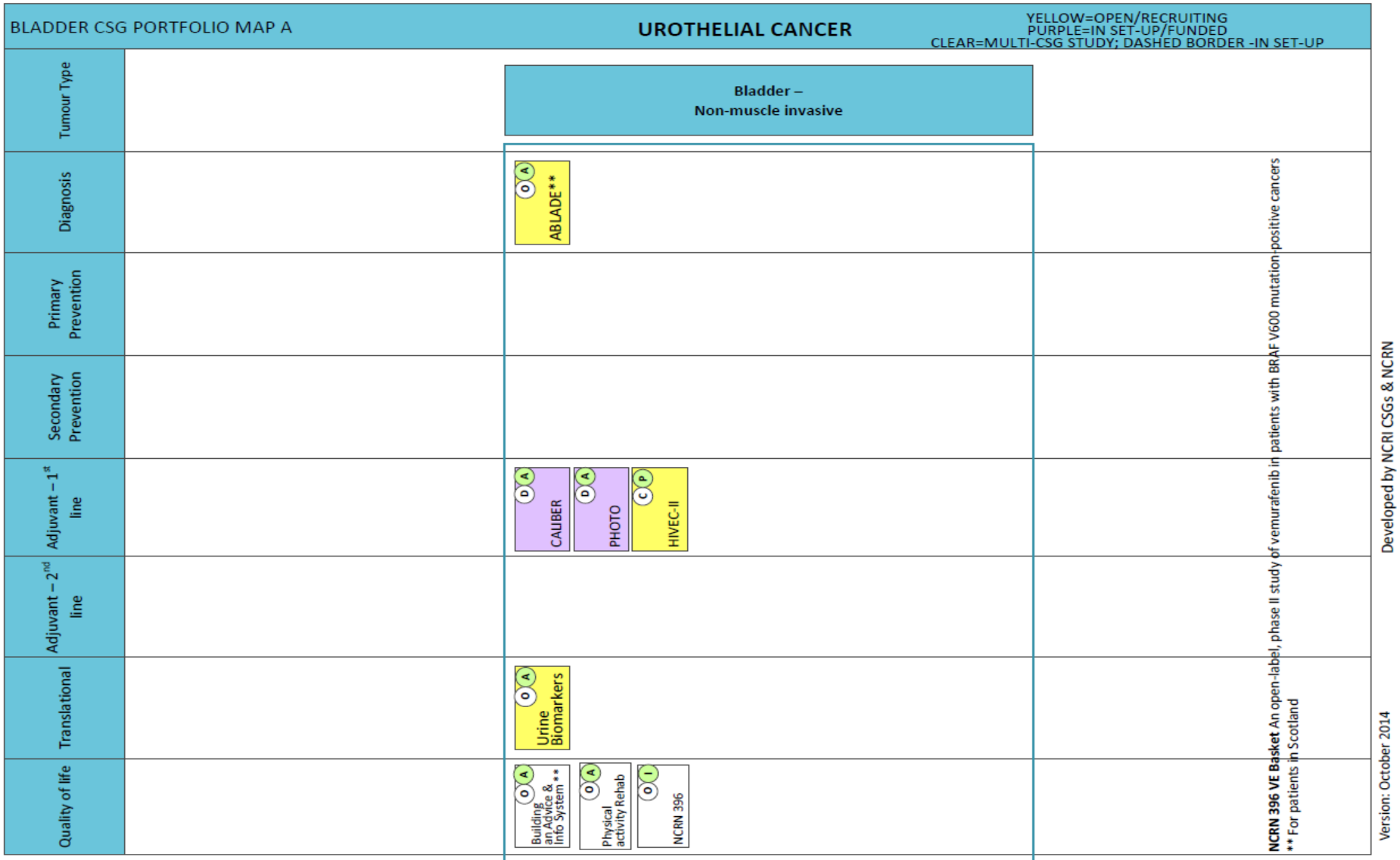
D – T2 & Below (TABS) Subgroup Strategy

The TABS Subgroup strategy is outlined below:

- To continue to foster and develop strong collaboration between surgical and non-surgical oncologists. Particularly for trials where surgical and non-surgical treatments are compared or where multimodality treatment involves operative and non-operative components
- To encourage research teams to present their ideas early to the group, to support the development of fundable, successful projects within a broad and active portfolio. The group will also encourage communication between TMGs for studies where there may be an apparent overlap between studies
- Continue to develop trials with a broad appeal to clinical units of all types. This strategy encourages wider engagement in research and provides opportunities for less active units and networks to get involved
- Trial ideas brought to the group are encouraged, but in addition the group will focus on 2 key areas which address key clinical questions for clinicians and patients:
    - Development of novel intravesical agents and strategies for high risk non-muscle invasive bladder cancer (particularly in an era of shortages of the standard treatment with BCG)
    - 2)QoL and survivorship issues - development of studies to assess HRQoL for treatments for bladder cancer with output to assist patient choice. Strong consumer representation is key to this area.

Appendix 3

Portfolio maps



BLADDER CSG PORTFOLIO MAP B
UROTHELIAL CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Diagnosis
Neoadjuvant
Surgery
Adjuvant/ Radiotherapy
Advanced Metastatic – 1st line
Maintenance
Advanced Metastatic – 2nd line
Quality of life/ TranslationI
Bladder – Muscle-invasive
Upper Tract UCC
Penile
ABLADE**
MARBLE*
COAST
NEOBLADE
HYBRID
TUXEDO
IDEAL
GemTrans
POUT
TOTEM
COAST
TOUCAN
FIESTA
VinCap
PLUTO
Urine Biomarkers
Building an Advice & Info System**
GI care bundle***
Physical activity Rehab
NCRN 396
Building an Advice & Info System **
Urine Biomarkers
Physical activity Rehab
NCRN 396
Building an Advice & Info System **
Urine Biomarkers
Physical activity Rehab
NCRN 396
PROM
NCRN 396 VE Basket An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers
* Incorporating an 18F-FLT PET substudy - Not open to additional sites.
**Open to patients in Scotland.
***Investigating pelvic chemoRT - bladder and cervix.
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

Appendix 4

Publications in the reporting year

BC2001

Huddart RA. Defining Bowel Dose Volume Constraints for Bladder Radiotherapy Planning, *Clinical Oncology* 2014

McDonald F, Waters R, Gulliford S, Hall E, James N, Huddart RA Defining bowel dose volume constraints for bladder radiotherapy planning . *Clin Oncol* (R Coll radiol) 2015.2791):22-9

BCON

Hunter BA, Eustace A, Irlam JJ, Valentine HR, Denley H, Oguejiofor KK, Swindell R, Hoskin P, Choudhury A, West CM. Expression of hypoxia-inducible factor-1alpha predicts benefit from hypoxia modification in invasive bladder cancer, *BJC* 2014, 1-7 doi:10.1038/bjc.2014.315

SUCCINT

Geldart T, Chester J, Casbard A , Crabb S, Elliott S, SUCCINCT: An open label, single arm non randomised phase 2 trial of gemcitabine and cisplatin chemotherapy I combination with sunitinib as first line treatment for patients with advanced urothelial carcinoma, *European Urology Platinum Priority Editorial* 20 Nov 2014

Birtle A. Heir to the throne or young pretender; can targeted therapy added to gemcitabine-cisplatin doublet therapy improve outcomes for advance urothelial cancer. *European Urology Platinum Priority Editorial* 20 Dec 2014

Geldart T, Chester J, Casbard A, Crabb S, Elliott T, Protheroe A, Huddart RA, Mead G, Barber J, Jones RJ, Smith J, Cowles R, Evans J, Griffiths G. An Open-label, Single-arm, Non-randomised, Phase 2 Trial of Gemcitabine and Cisplatin Chemotherapy in Combination with Sunitinib as First-line Treatment for Patients with Advanced Urothelial Carcinoma. *Eur Urol*. 2015 Apr;67(4):599-602. doi: 10.1016/j.eururo.2014.11.003. Epub 2014 Nov 20

BOXIT

Blazeby JM, Hall E, Aaronson NK, lloyd L, WatersR, Kelly JD, Fayers P. Validation and reliability teesting of the EORTC QLQ-NIMBC24 questionnaire module to assess patent –reported outcomes in non muscle invasive bladder cancer.2014 *Eur Urol* 66:1148-56

InPACT

Bogaerts, J., Sydes, M., Keat, N., McConnell, A., Benson, A., Ho, A. et al. Clinical trial designs for rare diseases: Studies developed and discussed by the International rare Cancers Initiative. *European Journal of Cancer*. (2015) 51:271-281

IDEAL

McNair HA, Hafeez S, Taylor H, Lalondrelle S, McDonald F, Hansen VN, Huddart R, Radiographer-led plan selection for bladder cancer radiotherapy: initiating a training programme and maintaining competency. *Br J Radiol*. 2015 Apr; 88 (1048):20140690. doi: 10.1259/bjr. 20140690. Epub 2015 Jan 7.

Hafeez S, Warren-Oseni K, McNair H, McDonald F, Lalondrelle S, Taylor H, Thompson A, Kumar P, Khoo V, Harris V. Tan M., Hansen V, Mohammed K, Thomas K, Jones K, Dearnaley D, Horwich A, Huddart R Prospective phase 1 study assessing feasibility of intensity modulated (IMRT) and image guided adaptive radiotherapy (IGART) to deliver simultaneous integrated high dose tumour boost (70Gy) for the treatment of localized muscle invasive bladder cancer J Clin Oncol 33, 2015 (suppl 7; abstr 307) (GU ASCO)

Appendix 5

Major international presentations in the reporting year

PLUTO

R Jones et al, TPS4589 Pazopanib versus paclitaxel ion relapsed urothelial tumours. A phase II study investigating pazopanib versus weekly paclitaxel in relapsed or progressive transitional cell carcinoma of the ureter, ASCO Annual Meeting, Chicago 2014

POUT

Wilson C, A B, Snape M, Lewis R, HALL E, Johnson M, Donovan J (2014). Recruitment challenges for trials of rare cancers: Lessons from the POUT trial for transitional cell cancer of the urinary system CRUK/11/027. NCRI National Cancer Conference; 2014; Liverpool:#B105

Wilson C, Rooshenas L, A B, Stein R, Hall E, Donovan J (2014). The uncertain case for adjuvant chemotherapy: lessons for recruitment from two pragmatic cancer trials (Optima HTA10/34/01, POUT CRUK/11/027. NCRI National Cancer Conference; 2014; Liverpool:#B108

IDEAL

Hafeez S, Koh M, Sohaib A, Huddart R, Assessing response to radiotherapy with diffusion weighted MRI (DW-MRI) in muscle invasive bladder cancer (MIBC), April 2014, ESTRO, Vienna

McDonald F, Hafeez S, Warren-Oseni K, Taylor H, Thompson A, Khoo V, Harris V, McNair H, Mohammed K, Thomas K, Jones K, Dearnaley D, Horwich A, Huddart R, Phase 1 dose-escalated image guided adaptive bladder radiotherapy study: Results of first dose cohort (68Gy) Jan 2014, GU ASCO

ODMIT C

Sylvester R.J., Oosterlinck W., Holmang S., Sydes M.R., Birtle A., Gudjonsson S., De Nunzio C., Okamura K., Kaasinen E., Solsona E., Ali-El-Dein B., Tatar C.A., Inman B.A., N'dow J., Oddens J., Babjuk M. Systematic review and individual patient data meta-analysis of randomized trials comparing a single immediate instillation of chemotherapy after transurethral resection to transurethral resection alone in patients with stage pTa-pT1 urothelial carcinoma of the bladder. EAU Annual Scientific Congress 2015.

HYMN

Kelly, J. State of the Art Lecture, European Urology Association Annual Scientific Meeting March 2015.

MARBLE

was presented at NCRI Liverpool on 3 November 2014 - title: Diffusion Weighted MRI to evaluate early treatment response in TCC of the bladder: MARBLE study. Authors; Pearson RA, Thelwall PE, Pieniazek P. Snell J, McKenna J, Heer R, McMenemin RM, Azzabi A, Pedley ID, Maxwell RJ, Plummer ER, Newell DR, Frew JA.

RAIDER trial

Lewis R, Hall E, Griffin C, Hafeez S, Huddart R (2014). Current UK practice in organ sparing treatment of muscle invasive bladder cancer (MIBC) and impact on design of the RAIDER image guided radiotherapy (IGRT) trial. NCRI National Cancer Conference; 2014; Liverpool:#36

Appendix 6

Strengths & weaknesses from the 2015 Progress Review

Strengths

- A good report, although a little repetitive in parts
- Positive and enthusiastic engagement with the panel
- Progress since the last review on the points raised at that time
- A well-functioning Group with strong leadership and good interactions between individuals
- Impressive degree of involvement from the research community, particularly urology
- Audit of research networks
- Good exploitation of, and interactions with the NIHR CRN
- Planned roadshows to boost recruitment
- Involvement of trainees in the group's activities and bringing on the next generation of researchers
- Good consumer involvement
- Interactions with the other urological CSGs and joint annual trials meetings
- A full portfolio (though somewhat crowded in some indications)
- A clear vision for the future with the direction of travel good and well thought through

Issues for the CSG to consider

- The panel would like the CSG to clearly define and prioritise the top 5 (or so) research questions of importance in bladder cancer, and their strategy for addressing them.
- In doing this, attention should be paid to the major competitive strengths of the UK: our network capacity and coordination; uniformity of the NHS service; ability to perform trials with randomised designs, etc.
- The Group's translational research should be strengthened, with closer engagement with basic and translational research groups and clear translational research objectives in the group's strategy and research designs.
- However, the group should also continue to pursue its goals of including research which addresses health service questions and addresses the quality of patient experience.