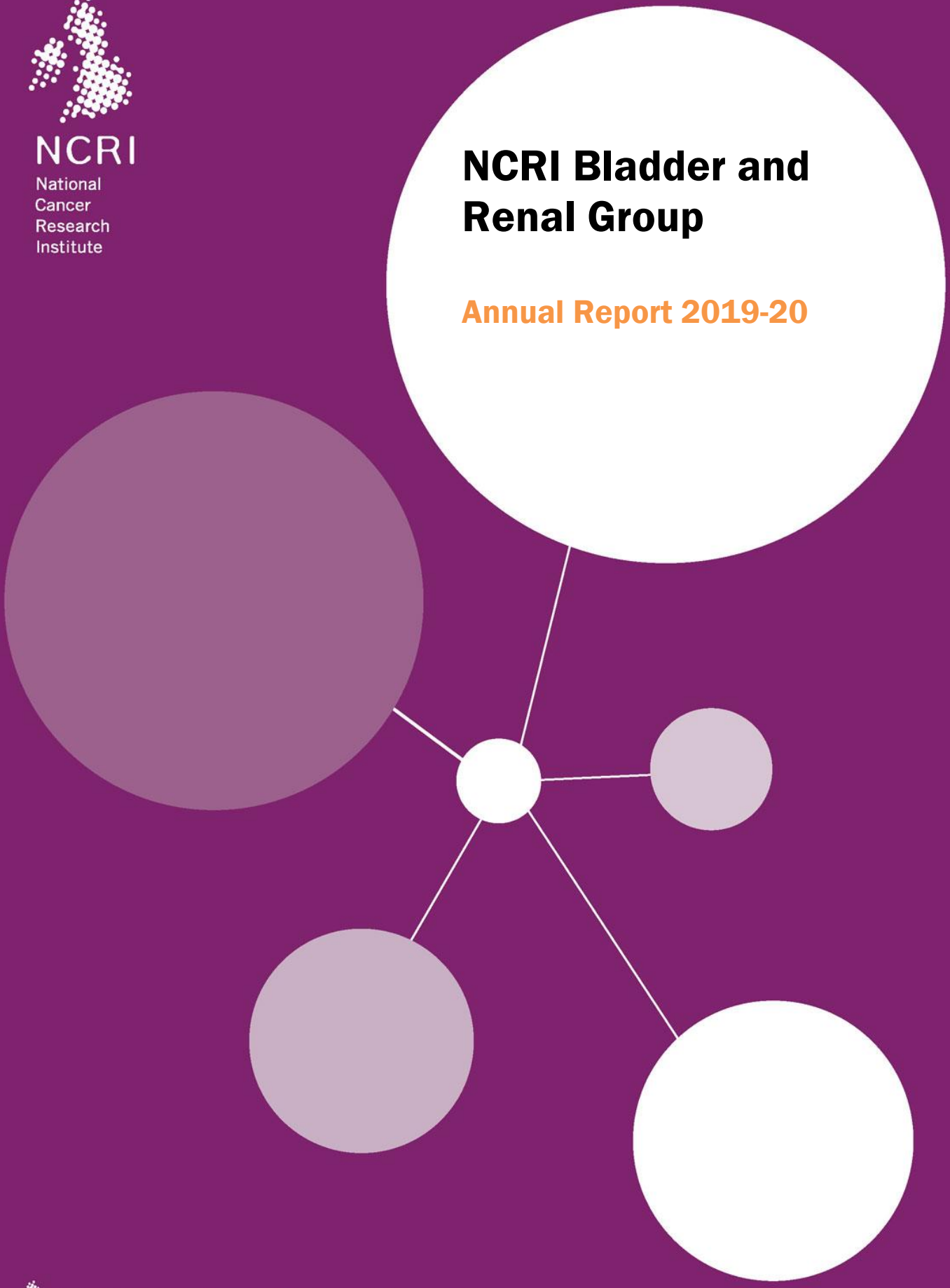
NCRI
National
Cancer
Research
Institute

NCRI Bladder and Renal Group

Annual Report 2019-20



Partners in cancer research

The NCRI Group Annual Reports 2019/2020 span the time period April 2019 – March 2020. The reports were submitted during a challenging time for all in the healthcare sector due to the COVID-19 pandemic. This has had an unprecedented impact on the activity of both the Research Group itself and wider research activities, ranging from the time available for research work versus clinical commitments to the funding of new trials and the recruitment of existing trials. Due to this the NCRI significantly extended the deadline for submission of annual reports and allowed the Groups to submit reduced reports, if time permitted, with the following sections at a minimum:

- Achievements (section 1 of the report)
- Funding Submissions over the last 12 months (section 5)
- Priorities and Challenges (section 7)

In addition to this, Consumer representatives of each Group were asked to only complete their sections if they feel able to. Most of our Consumers have submitted reports, however where reports have *not* been submitted this was due to extended periods of ill health, or additional work/home life constraints, as a result of COVID-19.

NCRI Bladder and Renal Group
Annual Report 2019-20

1. Top 3 achievements in the reporting year

Achievement 1

Presentation of primary outcomes from SORCE trial (oral abstract, ESMO 2019 https://doi.org/10.1186/ISRCTN38934710). This was the group's previous adjuvant treatment trial in renal cancer. Patients were randomised to three groups receiving 3 years placebo, 3 years sorafenib or 1 year of sorafenib and 2 years of placebo. The trial was negative for its primary outcome of relapse free survival. This was the last of 5 randomized phase III trials exploring VEGFRtki as adjuvant in this disease and one of 4 negative trials (2 of which exploring sorafenib). It was the only trial to explore extended duration of therapy. It was thus a practice-affirming trial in that the global consensus is that patients should not receive adjuvant sorafenib or any other VEGFRtki thus sparing unnecessary toxicity and cost, whilst enabling research / patient resources to focus on other studies exploring this unmet need (including the group's successor study, RAMPART, exploring two different immunotherapy treatments in the same niche).

Achievement 2

Formation (and early output from) a translational working party in bladder cancer. Our own formal consumer study revealed that better understanding of underlying biology was the single most important research priority for patients and the public with regards to bladder cancer. In light of this our bladder consumer representative, in collaboration with researchers within the group, and (crucially) other translational researchers, ran a half day satellite meeting prior to another bladder cancer research meeting. The purpose of this meeting was to set a research agenda in this domain but also to build a group charged with delivery of this agenda. This group was established in early March 2020 and will develop over the coming 12 months. Though separate to the NCRI group, it will report in to the main Group via it's overlapping membership.

Achievement 3

Presentation of primary outcomes from NEOBLADE (oral abstract, ASCO GU 2020 https://doi.org/10.1186/ISRCTN56349930). This was, we believe, the first randomised phase II trial ever to be conducted in the neoadjuvant treatment of muscle invasive bladder cancer. Improving neoadjuvant treatment has been an important goal of the group for several years, as we believe this is the best opportunity to improve cure rates for bladder cancer and the overarching strategy is to identify new drugs in advanced disease and fast track them into this setting. Although negative for the primary (surrogate) endpoint of Pathological Complete Response (pCR) rate, there was a tantalising survival benefit seen in the interventional group.

2. Structure of the Group

At the very end of the previous reporting period we agreed a change in structure of the subgroups to more closely align them with the disease issues, rather than medical specialisms, and to avoid unhelpful overlap between the groups. The subgroups are now: Urothelial Systemic Therapy Subgroup (chair: Professor Syed Hussain, Sheffield) (previously 'Advanced Disease'); Urothelial Local Therapies Subgroup (chair: Mr Param Mariappan, Edinburgh) (previously 'T2 and Below'); Renal Systemic Therapies Subgroup (chair: Dr Naveen Vasudev, Leeds) (title unchanged); Renal Local Therapies Subgroup (Chair Mr Axel Bex, London) (previously 'Surgical'); Penile Cancer (chair Dr Vincent Khoo, London) (title unchanged). The groups are actively encouraged to cross-fertilise in areas where joint working is essential (such as peri-operative systemic therapies and translational research).

Professor Bex (urologist, Royal Free) and Professor Pandha (medical oncologist, Royal Surrey) are new members of the Group. Prof Bex brings international experience from The Netherlands and in his role as lead for the European Organisation for Research and Treatment of Cancer (EORTC) Urology Group and Professor Hardev was appointed to support the groups desire to build strength in translational research. Mr Bex has now taken over from Mr Grant Stewart (urologist, Cambridge) as chair of the Renal Local Therapies Subgroup. Dr Simon Crabb (medical oncologist, Southampton) is back on the group.

Trainee members have been instrumental in developing the work around developing a consumer driven research agenda.

3. Bladder and Renal Group & Subgroup strategies

Bladder and Renal Group

This report has been updated to reflect the changes made to the Group's strategy early in the reporting year as described in last year's annual report.

Engaging with patients and the public in setting the research agenda

Building on the formal Public and Patient Involvement (PPI) research conducted previously, the Group has continued to place consumer involvement at the centre of its strategy. This research highlighted the particular priority placed by consumers on translational research. Led by Mr Henry Scowcroft (PPI member, London) the group organised a half day meeting as a satellite to a UK national meeting on bladder cancer translational research in Birmingham on 5th March 2020. This brought together several translational and clinical scientists, several of whom have not previously engaged with the Group. During the meeting it was established that a clear priority to explore novel markers of high risk non-muscle invasive bladder cancer should be a focus of the Group's ambition. This working Group will continue to meet virtually in order to develop this strategy further. Whilst this work focussed on bladder cancer, it mirrors ongoing efforts in renal cancer to follow a strategy developed based on formal needs assessment with significant consumer involvement.

Translational Science

In Renal cancer, the seminal work by our renal translational lead (Samra Turajlic) in renal cancer genomics has led to the development of a sub-study within The European Association of Science Editors (EASE) registry (TransEASE). The purpose of this study is to better understand the underlying biology of small renal tumours with the ultimate goal of being able to distinguish tumours which benefit from early surgical intervention and those which do not. In upper tract urothelial cancers, despite the termination of formal funding, we continue to progress plans to work with the valuable translational sample collection derived from the global practice-changing POUT trial. This is with a specific view to designing future trials in this niche. In bladder cancer we have continued to develop our pioneering precision medicine platform, ATLANTIS, where the genomic data derived from previous patients in ATLANTIS and its predecessor (LAMB) have been used to inform potential new targeted therapies. The strategy for ATLANTIS is to prove translational principles to be prosecuted in the curative (neoadjuvant) setting. GUSTO was funded this year and is the first precision medicine trial in the neoadjuvant setting which aims to use genomic classifiers to select patients for or against conventional chemotherapy. Note 'achievement 3' in this context. The main outcome of the Birmingham working group meeting was to prioritise the discovery of predictive biomarkers studies in non-muscle invasive bladder cancer and we envisage that this will become an important part of the future translational strategy of the group. Via this new partner-group we hope to work with a wider network of bladder cancer translational scientists.

To build a stronger portfolio of trials of local treatments

This remains a very active area of portfolio growth and development. In renal cancer, we are developing a novel chemo-embolisation trial (RAVE). The successor trial to POUT (currently named POUT2) continues to explore options in the management of upper tract urothelial cancer. Given the complexities and uncertainties regarding systemic therapies, we are setting up a working party to explore options for a surgical / staging trial. A study aiming to optimise follow up in renal cancer (RECUR renal) is also in development. In bladder cancer we have been considering new data from the Royal College of Radiologists which suggest that there are

significant access barriers to radical treatment in bladder cancer and we plan to explore these findings further to see how these can be broken down. One possible barrier is the prolonged pathway from presentation to radical treatment. The group has been active in advocating changes in the way NHS measure cancer waiting times in this regard and we look forward to the imminent removal of TURBT being regarded as 'first treatment' (rather than the diagnostic test it is for high risk disease). The BladderPATH study (which aims to remove TURBT from the pathway altogether), continues in its feasibility stage. Venturing into the opportunity to research routinely collected data, Scot BC is being developed within the Group to explore data from clinical practices across Scotland. iROC is successfully randomising patients between open and robot-assisted laparascopic cystectomy, and BRAVO concluded that a randomised study between cystectomy and BCG was unlikely to be feasible. In penile cancer, a study of MRI-PET pre-inguinal surgery has completed recruitment and a manuscript is being drafted for 2020.

Radiotherapy

RAIDER, a trial of adaptive radiotherapy in muscle invasive bladder cancer has completed accrual, and RADIO, an adaptive trial exploring novel radiosensitizers has begun. We have also developed studies using radiotherapy as an approach to systemic treatment: Re-ARM, which exploits the abscopal effect in metastatic urothelial cancer, is fully funded and due to start accrual in 2020 and a trial of systemic radium for bone metastases is in development. Hypofractionated focal radiotherapy is the subject of EQUATOR (oligometastatic renal cancer (VK – in development)), and NEST-X (treatment of primary RCC (KF – in development)).

Systemic Treatment

We have completed and reported first results from NeoBLADE (see 'achievement 3') in early bladder cancer. The next neoadjuvant study is now funded (GUSTO).
Rare tumours continue to be a focus for the Group and we are taking a leading role in The International Rare Cancer Initiative (IRCI) rare urothelial cancers group. AURORA (a study of immunotherapy in squamous cancer, SC, Southampton) has been invited to full application and there are advanced plans for a successor adjuvant treatment study in Upper Tract Urothelial Carcinoma (UTUC) (POUT2).

In renal cancer, we reported the final results of the SORCE adjuvant trial in renal cancer (see 'achievement 1'). Naxiva, a novel trial exploring VEGFRtki to surgically downstate locally advanced renal cancers, completed accrual to target and is currently being analysed. A successor study is in development.

We are also discussing a pan-disease study which aims to optimise immunotherapy scheduling (REFINE).

In penile cancer we completed VinCaP study has completed and a manuscript has been resubmitted to JCO post reviewers comments in March 2020.

Bladder Cancer Systemic Treatment Subgroup (Chair, Professor Syed Hussain)

Optimise systemic therapy by developing new drug hypotheses to test in MIBC

ATLANTIS remains the Subgroup's key study in advanced disease, designed to feed into a future study of neoadjuvant chemotherapy. This is a precision medicine maintenance study which currently has 3 nested randomised phase II trials directed by molecular selection markers. We anticipate that this study will be challenged in 2021 by the introduction of maintenance immunotherapy into routine practice. We are therefore exploiting the adaptive nature of the trial to introduce new randomisations which contain immunotherapy in both arms.
The GUSTO trial (funded this year, National Institute Health for Research (NIHR)) will test the principle of using molecular classifiers to determine choice of therapy in the neoadjuvant setting.

We have also reported NeoBLADE (see 'achievement 1').

Delivery of potentially practice changing studies

Following the success of the group's POUT study (reported last year), which defined the global standard of care in the postoperative management of UTUC, we have continued to develop the successor study, and an outline application to Cancer Research UK (CRUK) was successful. We continue to work with a major pharmaceutical partner to develop a precision-medicine adjuvant therapy study in this niche, although progress has been slowed by ambiguous results emerging from commercial trials in related areas.
The group has partnered with the Canadian research group to take part in BL-13, which aims to prove the value of adjuvant immunochemotherapy following radical radiotherapy for muscle invasive bladder cancer.
RADIO, an adaptive trial of systemic radiosensitizers in muscle invasive disease, which is the follow on study to the practice-changing BC2001 trial now has ethics approval and is in set up.
The group retains a leadership role in the IRCI rare urothelial cancers group (Dr Crabb, Professor Robert Jones are members). Within this group we continue to lead on the development of trials in rare histology (AURORA) and UTUC (POUT2).

Develop larger translational research programmes

ATLANTIS continues to provide a rich source of tissue for translation research in advanced disease. We are now carrying out a broad-panel Next Generation Sequencing (NGS) platform test on all patients which is providing rich information both at a descriptive level but also to leverage support from industry for discussing future trial options. Members of the group are part of the Birmingham Translational Working Party (see 'achievement 2'), although the initial focus of the group is now on non-muscle invasive disease.

Penile Cancer Subgroup (Chair, Dr Vincent Khoo)

Develop practice changing trials and optimise current practice procedures

The focus of the Penile Subgroup is to ensure UK wide representation, develop clinical practice changing trials and optimise current practice procedures. The past year has been successful. Several clinical studies have completed fully with publications and prepared manuscripts. The IRCI randomised phase III trial, INPACT passed its first recruitment threshold to continue the study. A new clinical trial is being developed for locally advanced and metastatic penile cancer.

There are two recent completed penile cancer studies:

- VinCaP study has completed and a manuscript has been resubmitted to JCO post reviewers' comments in March 2020.
- MRI-PET pre-inguinal surgery has completed recruitment and a manuscript is being drafted for 2020.

There is a major current randomised trial:

- The InPACT trial is Phase III International Penile Advanced Cancer Trial supported by the International Rare Cancer Initiative. This trial addressing several aspects in the radical management of penile surgery and radiotherapy/chemotherapy. The InPACT trial passed its first threshold of recruitment for trial continuation. At the end of 2019, 31/400 patients have been recruited. There are 14 trial centres and 8 more trial centres are being opened worldwide including USA, Canada, Mexico and Columbia. Trial recruitment in the UK was poor in 2019 but a recruitment strategy white paper has been developed to improvement involvement and recruitment.

The on-going strategic plans of the Penile Subgroup include ensuring replacement of research active members and representation from supra-regional penile groups nationally, maintaining efficient communication and information flow to local penile teams, recruiting appropriate consumer advocates as well as to develop and maintain international collaboration for new clinical studies.

Renal Cancer Local Treatment Subgroup (Chair, Dr Axel Bex (incoming) and Grant Stewart (outgoing))

Engage with BAUS and BAUS Oncology on promotion of their new trials

Robust links have been developed with BAUS Oncology for ensuring promotion of new surgical trials. At the British Association of Urological Surgeons (BAUS) Oncology meeting in November 2019, there were several talks highlighting trials and these were emphasised by the moderators in the discussion. There was also a breakout session at this meeting for our UTUC work.

Develop a range of surgery and radiotherapy relevant studies across all stages of renal cancer i.e. from screening to metastatic disease

The Subgroup continued this year on a strategy to develop trials for each stage of kidney cancer or upper urinary tract beginning from screening to follow up. Trials in progress are EASE, NEST, RAMPART, NAXIVA (completed), NEOAVAX.
EASE is a European active surveillance study which has opened in the UK and will not only reveal clinical data but translational exploratory data in cooperation with the Crick Institute, London. Unfortunately, we failed to secure CRUK funding for Trans-EASE but tissue collection is secured through the Crick and we continue to pursue research funding for the molecular analyses.
Other trials are yet at the level of proposal because they have either not secured grants or funding or are preliminary. This includes EQUATOR, a trial to evaluate focal ablative therapy in the treatment of oligometastatic disease, STARTs, a phase 3 study of ablative radiotherapy for small renal masses, RAVE, a study of preoperative vandatenib immobilisation of the renal artery in advanced Renal Cell Cancer (RCC), cytoreductive nephrectomy proposals and CONCERT, a cohort embedded trial of follow-up regimen based on RECUR data.

Deliver and complete feasibility studies in contentious areas to prove recruitment can be achieved

NEST, a feasibility cohort embedded trial of partial nephrectomy versus cryoablation is recruiting well ahead of target. The Subgroup expects full accrual in 2021. The Subgroup continues to discuss a possible extension with a radiotherapy arm (NEST-X).

Liaise with oncologists for neoadjuvant trials

This has been successfully accomplished in designing WIRE, a window of opportunity trial to investigate neoadjuvant targeted therapy and immunotherapy. In addition, NAXIVA, a neoadjuvant trial to downsize IVC thrombi with axitinib, was successfully completed and will report later this year.

Finally, NEOAVAX, a neoadjuvant trial with avelumab and axitinib, largely performed at the Netherlands Cancer Institute (NKI) in the Netherlands, has been discussed to open through oncology at Barts. Timelines are competitive and the trial may reach full accrual before opening through the subgroup. However, the Subgroup has made plans to cooperate with NAXIVA and NEOAVAX translational parts to assess impact of axitinib monotherapy versus combination with avelumab.

Bladder Cancer Local Treatment Subgroup (Chair, Mr Param Mariappan)

Enhance the outcomes of patients with high risk NMIBC (HR-NMIBC)

The focus of the group in April 2019 was the production of the 'research gap analysis' for the Strategy Day held in May 2019. The 'gap analysis' publication from the Kings College London (KCL) group formed the framework and material for this and, along with key information obtained from an online survey by our PPI, we produced a comprehensive list of "Research questions". These questions covered the whole spectrum of localised Bladder Cancer (BC), stratified into Diagnostic, Treatment and follow up aspects while incorporating themes of Quality of Life (QoL), timely personalised care, patient self-help, adapting to co-morbidities and good communication. A notable gap in our portfolio lay in Translational Research.

On the 5th March 2020, a group of bladder cancer investigators from multiple disciplines as well as bladder cancer (BC) patient and charity representatives, gathered at the University of Birmingham to discuss research priorities for BC from basic science and genomics to clinical trials and applied research. The overarching summary of this meeting was to highlight the need for a detailed investigation of the HR-NMIBC patient group was warranted, encompassing the comprehensive biomolecular examination of ex vivo biospecimens, the development of representative in vivo disease models, the investigation of promising novel therapeutics, and detailed qualitative and applied research.

Develop improved bladder sparing approaches in Bladder Cancer

BRAVO - is an RCT supported by TABS comparing BCG and radical cystectomy. Results of feasibility are to be presented at BAUS 2020. The study concluded that such randomisation using survival as an endpoint will be challenging to recruit into and patients will agree to be randomised if clinicians are in equipoise.

One recent submission to the EME programme for studies where input and support was received from the research group was the evaluation of radiotherapy in MIBC alongside biomarkers - The Christie's group, led by Professor Ananya Choudhury have received funding of £50k from NIHR to develop the Hypoxia marker into a usable platform - this work is progressing well and the group will re-submit for clinical trial funding.

Mr Rakesh Heer presented on a urinary mitochondrial DNA biomarker - BARCODE to TABS in Jan 2020. This test potentially allows for targeted surveillance unique to each patient. The initial process is DNA sequencing of the mitochondrial DNA to identify the index change in the whole genome from the primary tumour - this is then followed by simply downstream Polymerase chain reaction (PCR). T2 And Below Subgroup (TABS) (now Urothelial Local Therapies Subgroup) were fully supportive of developing this biomarker and an application to CRUK biomarker grant to develop preliminary data to power the full study.

Mr Hugh Mostafid presented a proposal for a trial using neo-adjuvant intravesical chemotherapy prior to TURBT. Using intravesical chemotherapy in this way is likely to improve compliance with chemotherapy as the current compliance to post-op instillation is poor. TABS supported the study while making suggestions on study methodology including considering a

cluster randomised controlled trial (RCT) to evaluate practice at sites and recurrence as end points.

Work with the Systemic Treatments Bladder Cancer Subgroup to improve neoadjuvant, concomitant and adjuvant therapies for patients with invasive urothelial cancer

The successful POUT trial is being followed by POUT2 exploring chemotherapy +/- I/O following nephroureterectomy - lead investigator and member of TABS, Dr Alison Birtle has been invited to submit a full application for funding from CRUK.

Another recent submission under the Efficacy and Mechanism (EME) programme, GUSTO led by TABS member Prof Jim Catto, is a randomised phase 2 trial employing stratified medicine in MIBC by identifying patients suitable for neo-adjuvant chemotherapy +/- I/O prior to radical surgery or radiotherapy on the basis of genomics. This application is progressing well and some details such as IP are being finalized at the moment - study was expected to open in the summer.

A trial to evaluate clinical effect and cost-effectiveness of oral anticoagulants for reducing risk of thromboembolic events in patients receiving neoadjuvant chemotherapy for Muscle Invasive Bladder Cancer (MIBC) led by Professor Husain was supported by TABS and submitted for Health Technology Assessment (HTA) funding this year. Having been unsuccessful, the study was re-discussed at main group meeting in Jan 2020 and will be re-submitted after some research-group guided revisions.

The BladderPath study, aims to accelerate the pathway between initial diagnosis and definitive treatment of MIBC by randomising patients into MRI (Magnetic Resonance Imaging) v TURBT (trans urethral resection of bladder tumour) pathways - this is an HTA funded trial which appeared slow to recruit and was potentially stopped by funders. This study was re-discussed at the main Group meeting in Jan 2020 and felt to still be a relevant, potentially practice-changing study and a letter of support given recommending continuation.

Seek to understand better and then improve, factors that impact on patient quality of life and experience of bladder cancer treatment

Yorkshire PROMS study - results are being presented at BAUS 2020. From 1,796 participants who completed surveys, 68.5% reported at least one problem in any EQ-5D-5L domain. The study concluded that differences exist between treatments and patient demographics that require exploration and improvement.

The chair of TABS (Mr Mariappan) is leading on a large project in Scotland building on the work with the Scottish Quality Performance Indicators (QPI). This project, Scot BC Quality Overall Progression free Survival (OPS) (Scottish Bladder Cancer Quality Performance Indicators influencing Outcomes, Prognosis & novel Surveillance) has several Work Packages - WP 1: Evaluating outcomes in Non-Muscle Invasive Bladder Cancer (NMIBC) to develop a non-existent contemporary risk-calculator. The first publication from this project, evaluating 4,246 patients has been reviewed by European Urology and is being revised for publication. The first risk calculator based on a 3-5 year follow up is expected to be ready by Nov. 2020; WP2: a

novel surveillance protocol for NMIBC has been developed, introducing less frequent cystoscopy and the use of PROMS and adopted across Scotland through the Scottish Access Collaborative. Funding of £50k has been received from the Scottish Govt. to develop a national database to prospectively collect clinical data; WP3: a translational research element where urine, blood and tissue samples will be prospectively collected for future testing of developing bio-markers within the prospective cohorts. This project was presented to TABS in Jan 2020 and felt to be covering several areas of the "research gap analysis" and received full support to seek funding from the Chief Scientist Office (CSO) and CRUK.

Renal Cancer Systemic Treatment Subgroup (Chair, Dr Naveen Vasudev)

Generate internationally competitive trials for all patients with advanced disease

The treatment landscape in patients with metastatic Renal Cell Carcinoma (mRCC) continues to evolve rapidly, presenting opportunities and challenges in study development.

The potentially practice-changing PRISM trial, examining alternative scheduling of combination ipilimumab plus nivolumab, has successfully completed recruitment ahead of target and is an exemplar of developing the right study at the right time.

What to do following failure on Immuno-Oncology (IO) is a key question and the group have successfully developed the CAPER trial (led by Dr Tom Waddell) that is due to open shortly, exploring the addition of cyclophosphamide to pembrolizumab following IO failure.

The group continues to actively engage with pharma and a number of other proposals have been submitted over the past 12 months. Three proposals were submitted to the recent IIT call by MSD, for example, but were not funded and we will continue to explore other opportunities.

WIRE, a window of opportunity trial to investigate neoadjuvant targeted therapy and immunotherapy has ethical approval and is due to open when the COVID-19 situation passes.

Develop pragmatic studies that are deliverable across the network

This is an overarching strategic aim and should also reflect priority areas for research identified by patients. Pragmatic studies such as STAR and PRISM, examining treatment duration or scheduling, have been successful. The group carefully considered a study proposal looking at the duration of immunotherapy in RCC (similar to studies in melanoma) but this was not considered feasible based on the sample size required. The possibility of incorporating a renal cohort in a basket study (led by colleagues outside the group) examining dosing frequency is being explored.

We have also recently discussed the idea of collecting real world data through a web-based database (eg REDCap). The group felt there was value in this, reflects consumer interests and is something potentially achievable by members and the wider renal community. Patients starting treatment following IOIO and patients with non-clear cell were considered, with the

former probably favoured. If successful, the potential to incorporate patient consent for prospective biobanking was discussed.

RAMPART has been recruiting well but is temporarily suspended due to COVID-19 but plans are in place to reopen the trial and mitigate the impact of the suspension.

Develop high quality translational biobanks with an identified network of basic scientists with relevant expertise to deliver biomarker studies

No biomarkers are in routine clinical use in patients with RCC. The establishment of high quality sample banks in the context of a changing treatment landscape is a priority. The need for standardisation of protocols/Standard Operating Procedures (SOPs), gaining generic consent and future-proofing is recognised by the group. In parallel, we intend to identify basic scientists with relevant and complementary expertise to co-ordinate high quality biomarker studies.

The TRIBE study (led by Dr Fiona Thistlethwaite) is a biomarker driven study to understand the influence of VEGF TKI on the immune environment prior to starting IO.

A pilot study (led by Dr Natalie Charnley) exploring the potential for Positron emission tomography (PET) as an early biomarker of response to nivolumab has almost completed recruitment of its first 10 patients and funding for a further 20 patients has been secured. Parallel studies exploring Computed Tomography (CT) density as a predictive biomarker are being explored.

PRISM incorporates a robust translational component, with longitudinal sample collection strengthened by collaboration for incorporation of cfDNA with Dr Samra Turajlic at the Crick Institute. Blood and tissue-based biomarker analyses are currently being planned.
The NIHR funded, portfolio adopted, multi-centre prospective RCC Biobank study represents a tremendous UK resource for diagnostic and prognostic biomarker studies, with collection of blood and tissue from >700 patients with newly diagnosed suspected RCC. The first two manuscripts from this study have recently been published.

Having a talented, ambitious and engaged Group membership consisting of experienced and lesser experienced investigators

The Group recently had their first face-to-face meeting in London (Feb, 2020). It was recognised that, whilst the existing format of monthly Friday morning TCs has been largely effective, not all members are able to dial in, limiting wider engagement. Therefore, moving forwards, the Group will meet less often (four times per year, including an annual Face to Face meeting), at varying times/days and with a focused agenda. There is an explicit expectation that all members engage with the activity of the group. Broad representation from across the UK is maintained, as well as a balance of experienced members who are able to advise and nurture more junior members, as exemplified by the number of new CIs currently leading their own studies. The group are also in the process of appointing a new Chair, since Dr Vasudev is due to rotate off the main Group this summer.

4. Task Groups & Working Parties

The Bladder & Renal Cancer Group had no task groups or working parties during the reporting year.

5. Funding applications in last year

Table 2 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK					
May 2019					
TransRAMPART: Renal Adjuvant MultiPle Arm Randomised Trial - Translational Research	Prospective Sample Collection Award	Dr Angela Meade	Conditionally supported		
RE-ARM: A Randomised phase II trial of Enhancement of efficacy of Atezolizumab by Radiotherapy in Metastatic urothelial cancer	Clinical Trial Award - Endorsement	Professor Robert Huddart	Conditionally Endorsed		
Molecular profiling to define small renal masses at risk for progression on active surveillance	Biomarker Project Award	Dr Samra Turajlic	Not supported		
November 2019					
POUT2: Chemotherapy with or without immunotherapy following nephro-ureterectomy for upper tract urothelial cancer	Clinical Trial Award - Outline	Dr Alison Birtle	Invited to full		
Targeted proteomic approaches to risk stratification in high-risk non-muscle-invasive bladder cancer: "TargetPro-HR"	Biomarker Project Award	Dr Douglas Ward	Not supported		

The delay between bladder cancer diagnosis and definitive treatment – how does it affect patient outcomes?	Project Award	Dr Mieke Van Hemelrijck	Not supported		
Other committees					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of Group input**	**Funding amount**
Platform Selection for Biomarker Directed Radiotherapy for Bladder Cancer	NIHR/ EME	Catharine West	Funded	Support	39,510.40
Genotype of Urothelial cancer: Stratified Treatment and Oncological outcomes (GUSTO): Phase II study	NIHR/ EME	Jim Catto (Group member)	Funded subject to conditions	Reactive discussions in Subgroup and main Group	Not known
The clinical effect and cost-effectiveness of oral anticoagulants for reducing risk of thromboembolic events in patients receiving neoadjuvant chemotherapy for Muscle invasive bladder cancer	NIHR / HTA programme	Syed Hussain (Group member)	Not funded	Reactive discussions in Subgroup and main Group	

6. Consumer involvement

Mrs Salena Mulhere, Ms Alison Fielding and Mr Henry Scowcroft

The Group are sorry to report the deaths of two influential patient advocates into bladder and renal cancer during the year. Andrew Winterbottom, the founder of Fight Bladder Cancer died in May 2019 and Pat Hanlon, a kidney cancer patient and advocate died in January 2020. Both had helped to advance awareness of urological cancers and to ensure that research was centred around patient needs.

The 2019/20 consumer team of Mr Scowcroft for Bladder and Ms Fielding and Mrs Mulhere for RCC have backgrounds of either being a patient or a partner of someone with cancer. Each also brings a useful background of knowledge and contacts gained from their work with Cancer Research UK, Fight Bladder Cancer and the kidney cancer charities. Mr Scowcroft sits on both Bladder Local and Systematic Treatment Subgroups, Ms Fielding on the Renal Local Treatment Subgroup and Mrs Mulhere on the Renal Systemic Therapy Subgroup. All of the consumer team are part of the Consumer Forum and have attended NCRI Conference and several forum events at which Dragon's Den sessions into research questions have taken place.

One joint piece of work has been to help ensure the Group's strategy is aligned to the priorities of patients and consumers. This involved building on previous research, incorporating the 'Living with and beyond cancer' NCRI James Lind Alliance Priorities, identifying possible gaps, and seeking wider input from the relevant communities. Each has also engaged in particular projects to further the Group's work programme.

Mr Scowcroft has continued to be involved in several trials, including part of the TMGs for DURANCE, POUT2, Re-ARM, and Exemplar studies, and is member of Fight Bladder Cancer research steering/strategy group.

He presented joint work on consumer priorities work at the Bladder & Renal 2019 strategy away day, identifying biological/translational research as an area in which we are relatively lacking. To build on this work, he co-convened and co-chaired, with Dr Rik Bryan and Dr Mieke Van Hemelrick, a Translational Bladder Cancer Strategy workshop – a closed forum of ~15 bladder cancer researchers, funders and patients – to define translational research priorities.

He has visited or spoken with several research groups to build relationships, including Rik Bryan in Birmingham to discuss his group's work on biomarkers, Dr Crabb and Professor Gareth Griffiths in Southampton about potential for platform bladder cancer studies, Dr Inigo Martincorena at Sanger Institute, Dr Jennifer Rohn at UCL, and Dr Van Hemelrijck at KCL. In addition, he gave a well-received opening talk at Translational Bladder Cancer Research Meeting in Birmingham in March 2020, attended CM-Path Biobanking workshop, and has taken up a freelance role as Patient Editor at BMJ, to improve representation of the patient voice in their scholarly content, editorial and opinion output.

Ms Fielding has taken an active part in the Bladder and Renal group meetings as well as contributing to the Living With and Beyond Cancer subgroup on co-morbidity. She has also attended Kings Fund conferences to gather and share data and information on best practice in this area. She has spent the year growing links into the kidney cancer patient community by discussions with Kidney Cancer UK and membership of their online community. A long standing supporter and volunteer for the Kidney Cancer Support Network, she is now a trustee of the organisation. Each of these has enriched and validated patient feedback. Plans to present research from an international Kidney Cancer Patient survey were shelved due to a change to the meeting agenda in March but will feed into future discussions.

She is a member of the Rampart and Naxiva Trial Management Groups and consulted on others outside of the main group meetings. At the time of writing, this work included consultations on the information to patients and a video for improving the consultations between urologists and patients regarding the trial. Consumers were also consulted on the process for suspending Rampart and conditions for re-starting recruitment and treatment post COVID-19. This has obviously been a concerning area for patients.

Mrs Mulhere is also a member of the Rampart Trial Management group and has accepted a place on the CAPER Trial Management Group. She is also part of the Cancer Research UK Cancer Insight Panel on research and strategy. As part of this, she has undertaken several speaking engagements with Cancer Research UK to discuss the value of consumer involvement and give her insight into caring for someone with kidney cancer.

The team feel that there is still work to be done on developing more projects on bladder and kidney cancer following COVID-19. They are looking forward to engaging further with clinical colleagues to identify, scope and support future studies.

7. Priorities and challenges for the forthcoming year

Priority 1 Delivering translational strategy in early (NMI) bladder cancer, as set out at the Birmingham 2020 meeting. The 'arms-length' working party set up at this meeting, though disrupted by current events, will continue to develop a strategy to deliver the proposed agenda for biomarker discovery in NMIBC.
Priority 2 Consolidate plans for a viable successor to POUT. Although the focus to date has been on developing a successor drug trial, current developments in advanced urothelial cancer mean that this is complex and negotiations with drug companies have been slow because of these complexities. Whilst these discussions continue, the Group has initiated broader discussions to consider other opportunities for a trial in UTUC. POUT itself was born of similar discussions with the (then) Bladder and Renal Group.
Priority 3 In renal cancer we recognise the need to build an evidence base around the use of stereotactic radiotherapy as radical treatment for small renal primaries as we recognise that the UK is uniquely poised to do this as it becomes established as an otherwise poorly-understood niche treatment option. The NEST-X and START studies are in development, but the local treatments subgroup is charged with consolidating a strategy to ensure an opportunity to develop level one evidence is not missed.
Challenge 1

Patients and the public setting the research agenda: continued development. This is a key strategy policy of the Group which is already working. The Group recognises the need to maintain and review this engagement.
Challenge 2 A new pragmatic trial in NMIBC remains elusive. This has been an area of success for the group in the past, but there are currently no immediate plans for a successor study.
Challenge 3 Recovery from the impact of COVID-19. At the time or writing, all studies remain closed to accrual, grant funding opportunities have been withdrawn and clinical services are considering re-emergence from hibernation to address a likely backlog of undiagnosed cancer cases. The realisation that COVID-19 will remain in the healthcare system for many months to come makes it difficult to plan full recovery for clinical services and research services.

8. Collaborative partnership studies with industry

Our Subgroup structure lends itself to close working with industry. As described above, we have numerous investigator-sponsored studies which are conducted in partnership with industry. To highlight a few: the RAMPART adjuvant phase III renal cancer study (AstraZeneca); NeoBLADE adjuvant bladder cancer (Boehringer); ATLANTIS (multiple partners). The group retains close links with the Experimental Cancer Medicine Centres (ECMC) and has capitalised on these links to deliver early phase studies (eg. SPIRE (SC)).

9. Appendices

Appendix 1 – Bladder and Renal Group and Subgroup strategies

- A – Bladder and Renal Group Strategy
- B - Bladder Cancer Systemic Therapies Subgroup Strategy
- C – Penile Cancer Subgroup Strategy
- D – Renal Cancer Local Therapy Subgroup Strategy
- E – Bladder Cancer Local Therapy Subgroup Strategy
- F – Renal Cancer Systemic Therapy Subgroup Strategy

Appendix 2 – Top 5 publications in reporting year & Group involvement with NICE appraisals

Professor Rob Jones (Bladder and Renal Cancer Group Chair)

Appendix 1

Bladder and Renal Group & Subgroup Strategies

A – Bladder and Renal Group Strategy

At our 2019 Strategy Day it was agreed that our overall aim will be:
Developing the highest quality clinical and translational research portfolio that integrates patient led priorities, improves patient outcomes and gives new insights into the diseases we treat.

We identified 5 areas that we wish to focus on to deliver this challenge.

1. Engaging with patients and the public in setting the research agenda

The Group agreed that we should work to ensure that those areas of priority to our patients are reflected in our research development portfolio.

Our Bladder and Renal Group cancer patient representatives (Alison Fielding, Salena Mulhere, Henry Scowcroft) together with our trainee Dr Arabella Hunt, are building upon an RCC patient RCC gap analysis (led by Group members Mr Grant Stewart Dr Janet Brown and their teams in Cambridge and Sheffield) to identify patient priorities for research in both bladder cancer and renal cancer.

Preliminary conclusions indicate that patients want research to reveal a greater understanding of disease biology that will lead to novel treatments; develop improved screening, surveillance and diagnostic methods; and identify optimal sequences of treatments. These observations require substantiating in larger studies with broader engagement. We will therefore establish a Patient Priority Working Group to deliver a more data-led robust understanding of patient priorities. These will then instruct initiatives to ensure consumer priorities are reflected in the portfolio.

We are aware that there are many patients who are excluded from interventional clinical trials, frequently due to their co-morbidities or due to resource limitations at their treating centre. There are many issues regarding patient experience before, during and after treatment that we need to understand better. The patient priority working party will develop a program of qualitative research that aims to improve access to clinical trials for the majority of patients who are not able to contribute to current interventional studies.

2. Translational Science

It is a priority for the Group to ensure that we learn as much as possible from our clinical trial activity about the biology of the diseases we treat as well as the mechanisms of efficacy and toxicity of our treatments. We wish to avoid translational work that pays lip service to the expectation that clinical research requires a translational component. The reality is that a range of pre-clinical expertise will be required across our portfolio and that the breadth of skills

required will not be reflected by the Group membership. We therefore wish to establish a Translational Working Party led by Dr Samra Turajlic that will identify a network of high quality translational scientists working in areas relevant to bladder and renal cancer pre-clinical research. This resource will ensure that relevant pre-clinical scientists are invited to contribute to projects in development at the earliest possible stage. The Working Group will also develop a generic component for trial consent forms, influenced by Dr Turajlic's experience with the TraceRx and PEACE studies, that will ensure future-proofing for biological samples and data generated from our trial activity.

3. Local Treatments

The Group will be reorganised to have Bladder and Renal Local Treatment Subgroups. These will replace the current Bladder T2 & Below (TABS) and the Renal Surgical Subgroup. They will support study development with surgical and non-surgical local treatments including radiotherapy and other modalities such as RFA and cryotherapy. This clarifies the activities of the subgroups. Local treatments often provide rich opportunity for translational work given that acquisition of tumour material is frequently a standard of care. The membership of each local treatment subgroup will be reviewed to ensure that a translational scientist is a group member.

We believe there is opportunity for the many patients in the country who undergo surgical procedures and who are not eligible for studies on our interventional clinical trial portfolio to contribute to our understanding of their experiences through qualitative and semi-quantitative research. The local treatment subgroups will therefore explore whether there are opportunities with BAUS to develop studies that are relevant for a wider population of patients and the patient priority working party will develop activity in this area.

4. Radiotherapy

Radiotherapy is a mainstay of treatment for many bladder cancer patients. Efficacy needs to continue to be increased and toxicity decreased. Radiotherapy increasingly dovetails with other therapeutic modalities, and with the advent of new systemic therapies the role of combination systemic treatment and radiotherapy needs to be developed. The UK has led the world in the field of chemoradiotherapy in bladder cancer, and we intend to build on this success. The Group prioritises delivery of radiotherapy research in these areas and therefore will ensure clinical oncology expertise within our local and systemic treatment subgroups in bladder and RCC.

We will develop studies that a) continue to refine methodology with highly technical radiotherapy b) are pragmatic ensuring improvement of radiotherapy regimes that are current standards of care c) explore radiotherapy in combination with systemic treatments and d) address areas of high unmet clinical need including management of brain metastases.

5. Systemic Treatment

The Advanced Bladder Cancer Subgroup has been renamed to the Bladder Systemic Treatment Subgroup and, along with the Renal Cancer Systemic Treatments Subgroup, leads our development of novel systemic therapies and combinations in both diseases. Both groups are productive, have successfully developed potentially practice changing clinical trials that are on the portfolio and meet regularly. We plan to build upon this success with continued development of studies with new agents in areas of unmet clinical need. We also recognise the importance of development of predictive biomarkers of response and toxicity and will ensure activity in this area alongside our interventional studies. We wish to widen access to interventional clinical trials by developing more pragmatic studies that are deliverable in all centres across the network enabling access for a wider patient population.

B - Advanced Bladder Cancer Subgroup (Chair, Professor Syed Hussain)

Optimise systemic therapy by developing new drug hypotheses to test in MIBC

Efficient delivery of proof of concept studies in advanced disease exemplified by the development of the ATLANTIS precision medicine platform in the maintenance therapy setting (co-CIs Rob Jones & Thomas Powles). New biomarker driven randomised cohorts are being added into this multi arm study successfully, each with a named lead investigator (Rob Jones, Tom Powles, Simon Crabb, Syed Hussain). As the trial develops, we hope to engage with young investigators in this role. Increasing number of centres (currently 29) are recruiting into this national trial.
The subgroups strategy is to use ATLANTIS to identify new drug signals before developing those signals in the neoadjuvant setting: the setting where the UK previously demonstrated that systemic therapy can improve the cure rate for muscle invasive bladder cancer.

Working towards options of trials of neoadjuvant therapy through successful recruitment in studies in this clinical setting. NeoBlade trial (CI Syed Hussain) and ABACUS (CI Thomas Powles) completed recruitment successfully in 2018. Current examples of recruiting trials include SPIRE (CI Simon Crabb). Current example of study in development in neo-adjuvant setting is GUSTO (CI James Catto, CO-I Simon Crabb, Syed Hussain). This is a phase 2 RCT evaluating the use of genomic profiling in guiding neoadjuvant treatments currently under review (at the Urothelial Cancer NIHR-EME call). The trial, if funded, will investigate real time genomic profiling by randomising 320 patients to either standard care (neoadjuvant chemotherapy and radical cystectomy) or genome stratified care.

Working in collaboration with industry to deliver high quality trials of novel agents in areas of unmet need. In addition to the multiple examples on which we have published (e.g., LaMB, PLUTO; TOUCAN; SUCCINCT; TOTEM; FIESTA) and examples of studies recently completed recruitment successfully include NeoBlade, ABACUS. Current examples of trials in recruitment include ATLANTIS, SPIRE.

We have further trials in development involving collaborations with pharma partners.

- RADio study is combining Durvalumab with Mitomycn C and 5-FU concurrent with radiotherapy (CI Nick James, CO-I Syed Hussain & Maria De Santis)
- EARL trial: A randomised phase II trial of enhancement of efficacy of atezolizumab by radiotherapy in metastatic urothelial cancer (CI Robert Huddart)
- Gareth Griffiths submitted an EOI to create a new Working Group within International Rare Cancer Initiative (IRCI) in non-TCC of the bladder on behalf of the Group and within it proposed a randomised phase II study utilising IO.
- POUT2. Building on the success of POUT, a further randomised phase III trial investigating the role of IO when added to adjuvant chemotherapy in upper tract urothelial cancer. This trial is also under discussion within the IRCI collaboration with several international parties wishing to take part.

Delivery of potentially practice changing studies

Implementing POUT, the first ever randomised phase III trial of adjuvant therapy in upper tract TCC. Trial is in development of a successor study POUT 2.

Develop larger translational research programmes

Utilisation of the ATLANTIS sample sets to allow generation of data on biomarker rates to facilitate new hypotheses to include in the new comparisons within ATLANTIS and other trials. Developing biomarkers of response utilising BC2001 trial sample set.

Entry of bladder cancer patients into the 100,000 Genomes Project and going forward to begin analyses of data emerging from this project.

Coordination of a collaborative approach to utilisation of samples sets from the Subgroup's prior and ongoing studies.

C - Penile Subgroup (Chair, Dr Vincent Khoo)

Develop practice changing trials and optimise current practice procedures.

The past year has been successful with the completion of several clinical studies, maintaining an international randomised phase III trial and further development of new potential studies in this rare cancer entity. We are also pleased to welcome David Wilkinson as our new consumer representative to join Neil Walker.

In the evaluation of penile nodal disease pre-surgery, two studies have been completed.
The first study aims to assess the use of MRI-PET for inguinal nodal staging (Asif Muneer). This study has completed recruitment of 46 cases for impalpable disease and 26 cases for palpable inguinal disease. The results are currently being analysed.

The second study aims to assess the feasibility of Sentimag®/Sienna+® injection for detecting Inguinal Sentinel Node involvement in penile cancer compared to standard of care (SOC) radioactive nanocolloid (Vijay Sangar). This study has also completed recruitment. The preliminary results report good concordance of Sienna with SOC agents which permits this technique to be considered for routine practice and allow units without nuclear medicine facilities to undertake sentinel node biopsy in penile cancers. An abstract is in preparation for 2019.

In the management of morbidity post-inguinal surgery, a randomised controlled phase II study is exploring funding opportunities to assess the efficacy of low-intensity shock wave therapy post inguinal lymph node dissection to lower surgical complications (VS).

In the management of radical penile cancer, the InPACT trial which is a randomised Phase III International Penile Advanced Cancer Trial supported by the International Rare Cancer Initiative, continues to recruit. This trial is ambitious and complex addressing several aspects in the radical management of penile surgery and radiotherapy/chemotherapy. The InPACT trial continues to recruit slowly but steadily worldwide in USA, Europe, Canada and Australia. Involvement of other countries in South America are being explored. In the UK, 4 of 6 centres are open. At the end of 2018, 16/400 patients have been recruited. It is part of the International Rare Cancers Initiative.

In the management of advanced penile cancer, one study (VinCaP) has been fully completed. The VinCaP study was a multi-centre Phase II trial of Vinflunine chemotherapy in locally-advanced and metastatic carcinoma of the penis that reported a clinical benefit rate (CBR) of 45.5% with an objective response rate of 35.5%. This study was awarded both an ASCO GU and ASCO presentation (LP). This study has been written up and will be submitted shortly (SN). Another industry supported study is being developed by AB. This phase II trial of standard of care (SOC) chemotherapy in combination with Immunotherapy (cemiplimab) in locally advanced or metastatic penile carcinoma follows the VinCaP trial design. This study is being finalised and is aimed to open at the end of 2019.

The other strategic plans of the penile subgroup include providing representation from research active penile groups nationally, ensuring efficient communication and information flow to local penile teams, to enable adequate patient advocate representation and to develop and maintain international collaboration for new clinical studies.

D - Surgical Subgroup – (Chair, Dr Axel Bex)

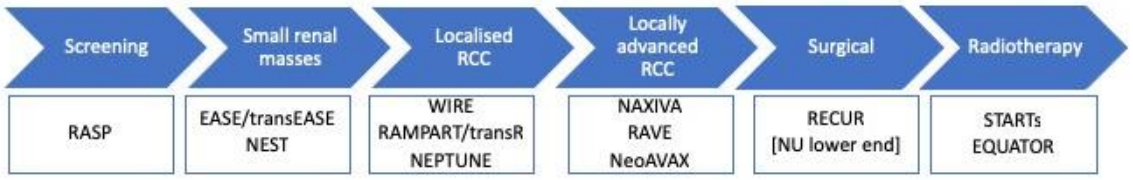
Engage with BAUS and BAUS Oncology on promotion of their new trials

BAUS, via President Elect Tim O'Brian, and BAUS Oncology, via Section Chair Ben Challacombe, have pledged to increase their level of support of RCC trials. BAUS have started to allow emails detailing new clinical trials in the field to be circulated e.g. RAMPART. This engagement has allowed new sites to be identified and for surgeons to be educated in the nuances of recruitment of patients within their clinics which is often new to them. The BAUS Nephrectomy

Audit will this year evaluate UK cytoreductive nephrectomy practice, there is interest in development of a cytoreductive nephrectomy clinical trial using the evidence from this audit. As such, it is anticipated that there will be greater collaboration between BAUS and the Group in the future.

Develop a range of surgery and radiotherapy relevant studies across all stages of renal cancer i.e. from screening to metastatic disease.

This aim is being achieved as demonstrated in the chart below of clinical studies that are recruiting or in development via the subgroup. This is in contrast to the situation in 2015 where there were zero surgical trials available.



Deliver and complete feasibility studies in contentious areas to prove recruitment can be achieved

There is international interest in the optimal management of small renal cancers. The NEST study (CI-Miss Maxine Tran) will start recruitment in Q2 2019. This cohort embedded study will evaluate feasibility of randomising patients to ablation or surgery for management of small renal cancers. Initially this will be a single centre study (at Royal Free Hospital, London) with the UK's largest renal cancer practice, as such the ideal centre to determine feasibility.

Dr Vincent Khoo is developing a protocol (EQUATOR), in conjunction with surgeon colleagues, to evaluate stereotactic radiosurgery for oligometastatic RCC. As part of the development of this study Dr Khoo has undertaken extensive scoping of feasibility of delivery be engaging with colleagues across the UK.

Liaise with oncologists for neoadjuvant trials

Surgical Subgroup members have led the development of a range of neoadjuvant trials in close collaboration with oncology colleagues.

1. NEOAVAX: Neoadjuvant axitinib+avelumab in localised RCC (CI-Mr Axel Bex; recruiting)
2. NAXIVA: Neoadjuvant axitinib in patients with IVC tumour thrombi (CI-Mr Grant Stewart; recruiting)
3. WIRE: Window-of-opportunity platform for novel drug combinations in surgical RCC patients (CI-Mr Grant Stewart; IRAS submission stage)
4. RAVE: TKI loaded embolization beads for selective embolization of patients with locally advanced RCC prior to surgery with the aim of assessing the immune stimulation following this process (CI-Prof David Nicol; protocol development)

E - T2 & Below (TABS) Subgroup – To be renamed Bladder Cancer Local Treatment Subgroup (Chair, Mr Param Mariappan)

Enhance the outcomes of patients with high risk NMIBC (HR-NMIBC)

The TABS subgroup aspires to have 'a study for every patient' – with the vast majority of cancers being within the surgical remit. Our strategy includes enhancing engagement with urologists in pragmatic trial development by emulating trials like PHOTO and HIVEC II.

Whilst intravesical BCG remains the Standard of Care (SoC) in HR-NMIBC, recent threats of global shortage and the need to embrace stratified medicine consequent to heterogeneity, several avenues have been explored.

The strongly supported HIVEC III proposal (Heated Mitomycin V BCG) failed to receive funding from the HTA and industry. The lessons learnt have now helped the team (with support from ICR-CTSU) explore a MAMS-style trial allowing for several experimental arms (novel and future) to be evaluated against SoC while ensuring a pragmatic approach.

There are several industry-driven I/O trials in HR-NMIBC where UK centres have opened to recruitment recently:
(a) POTOMAC - phase 3 RCT evaluating the safety and efficacy of Durvalumab+BCG V BCG.
(b) CheckMate 9UT - Nivolumab Vs Nivolumab+experimental medication (BMS-986205) +/- BCG in BCG un-responsive HR-NMIBC.

Trials in development - En-Bloc TURBT V standard TURBT could reduce the risk of recurrence and improve staging – the Group has given recommendations and awaits further details.

Develop improved bladder sparing approaches in muscle invasive bladder disease

The recent call from the EME programme for studies in Urothelial Carcinoma (UC) was discussed by TABS and proposals for 4 studies were submitted.

GUSTO, a randomised phase 2 trial employing stratified medicine in MIBC by identifying patients suitable for neo-adjuvant chemotherapy and/ or I/O prior to radical surgery or radiotherapy on the basis of genomics has been successful through the first stage of the selection process. Consequent to the recognition that not all MIBC patients respond to the standard-of-care neo-adjuvant chemotherapy, the trial is designed to introduce targeted treatment based on translational work demonstrating that tumours which are of basal-type are likely to respond to neo-adjuvant chemo while luminal-type tumours might respond to I/O.

The Bladder & Radiotherapy workshop in 2018 revealed a desire for 'platform type trials' as the preferred model and to evaluate radiotherapy in MIBC alongside biomarkers. Hypoxia markers were felt to be the most relevant - following submission to the EME, the team from The Christie

are applying to the NIHR to fund development of the biomarker before re-submission for clinical trial funding.

The RAIDER trial (Phase 2 RCT comparing adaptive image-guided standard radiotherapy V dose escalated tumour boost) is expected to complete recruitment soon.

Work with the Systemic Treatments Renal Cancer Working Party Strategy to improve neo-adjuvant, concomitant and adjuvant therapies for patients with invasive urothelial cancer

The hugely successful POUT trial is to be published soon, representing a good example of surgical and oncological collaboration in the Urothelial Carcinoma - a successor trial proposal is currently under review by CRUK CRC and an industry partner. The trial has been accepted into the portfolio of the newly formed IRCI group on rare urothelial cancers, with interest for collaboration from Australasia and Europe.

NEOBLADE, a phase 2 UK RCT of neoadjuvant treatment (comparison between Gem-Cis neoadjuvant chemotherapy and combination of chemotherapy and the Tyrosine Kinase Inhibitor, Nintedanib in MIBC) was supported by the Group and we are pleased to note has closed to recruitment in 2018.

There are several industry-driven I/O trials in MIBC where UK centres have opened to recruitment recently/ in setup:

(a) NIAGARA - Phase 3 global RCT evaluating efficacy and safety of combined neoadjuvant Gem-Cis chemotherapy and Durvalumab with adjuvant Durvalumab V neoadjuvant Gem-Cis chemotherapy alone prior to radical surgery.

(b) CheckMate 274 - phase 3 RCT evaluating DFS following adjuvant treatment with Nivolumab V placebo in patients with high risk of recurrence following radical surgery for bladder or upper tract urothelial carcinoma.

Trials in development that were presented to the Group - evaluation of Urinary Derived Lymphocytes (UDLs) as surrogates of the bladder immune TME could be used to predict response to IO drugs and prognosis - Group was supportive and has sought more details of the proposal.

Seek to understand better and then improve, factors that impact on patient quality of life and experience of bladder cancer treatment

The Life in Bladder Cancer study, funded by Yorkshire Cancer Research is evaluating the QoL in patients diagnosed with bladder cancer over the past 10 years using a questionnaire - recruitment is good following recent protocol amendments. Likewise, the Q-ABC study, evaluating QoL in patients undergoing treatment for MIBC, supported by the Group and developed by a trainee member opened to recruitment in 2018.

TABS have felt that Bio-marker development is essential to replace QoL-affecting surveillance cystoscopy - a proposal was submitted following the EME call. This proposal was based on the

UroMark and AmpseqUR urine-based tests with high levels of accuracy - unfortunately the submission was unsuccessful, and feedback will be shared with the Group. Nonetheless, DETECT II trial (using UroMark) should be completing recruitment soon.

The TABS members have been working on the research gap analysis for the Strategy Day meeting in May 2019. Support was received from the epidemiological researchers at KCL who have already performed the gap analysis using input from BAUS, BUG, charities and patient representatives. The TABS trainee member (with a mentor Group member) have been tasked to produce the details of the research gaps prior to the next TC on the 5th April 2019.

F - Renal Cancer Systemic Treatment Subgroup (Chair, Dr Naveen Vasudev)

Generate internationally competitive trials for all patients with advanced disease

The treatment landscape in patients with metastatic RCC (mRCC) continues to evolve rapidly, presenting opportunities and challenges in study development.

1) The potentially practice-changing PRISM trial, examining alternative scheduling of combination ipilimumab plus nivolumab, has been highly successful, with recruitment ahead of target and is an exemplar of developing the right study at the right time.
2) What to do following failure on IO is a key question and the group have successfully developed the CAPER trial (led by Dr Tom Waddell) that is currently in set-up, exploring the addition of cyclophosphamide to pembrolizumab following IO failure.
3) There is a significant unmet need for better treatment options for patients with non-clear cell RCC and this is a focus for the group moving forwards.

Develop a multi-arm platform second-line study

This is an ambitious but important strategic aim for the group. The past year has seen significant progress in the development of this concept (led by Dr Stefan Symeonides) with an intention to explore biomarker-driven stratification and would be internationally competitive. Study design has been agreed and initial arms have been identified

Develop high quality translational biobanks

No biomarkers are in routine clinical use in patients with RCC. The establishment of high quality sample banks in the context of a changing treatment landscape is a priority.

1) The TRIBE study (led by Dr Fiona Thistlethwaite) is a biomarker driven study to understand the influence of VEGF TKI on the immune environment prior to starting IO.
2) A pilot study (led by Dr Natalie Charnley) exploring the potential for PET as an early biomarker of response to nivolumab has recently opened to recruitment.
3) PRISM incorporates a robust translational component, with longitudinal sample collection strengthened by collaboration for incorporation of cfDNA with Dr Samra Turajlic at the Crick Institute.

4) The NIHR funded, portfolio adopted, multi-centre prospective RCC Biobank study represents a tremendous UK resource for diagnostic and prognostic biomarker studies, with collection of blood and tissue from >700 patients with newly diagnosed suspected RCC. The first manuscript from this study has recently been submitted for publication to Eur Urol Oncol.

Having a talented ambitious group membership consisting of experienced and lesser experienced investigators

The group's membership has continued to expand over the past twelve months, with involvement of a consumer member (Salena Mulhere), a trainee member (Dr Manon Pillai) and other medical oncologists with broad representation from across the UK. The group maintains a balance of experienced members who are able to support and nurture more junior members, as exemplified by the number of new CIs currently leading their own studies. The group continues to engage by monthly hour-long teleconferences.

Appendix 2

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	Group involvement in the trial
Rossi SH, Fielding A, Blick C, Handforth C, Brown JE, Stewart GD. Setting Research Priorities in Partnership with Patients to Provide Patient-centred Urological Cancer Care. Eur Urol. 2019 Jun;75(6):891-893	Documents some of the background work done by the group (and its predecessors) to develop a framework for PPI involvement in research agenda setting.	Designed, driven and delivered by the group and its predessors.
Challapalli A, Pearson S, Mitra AV, Coe M, Thomson A, Elliott T, Kirkbride P, Pickering L, Kirk H, Foulstone E, Evans H, Bravo A, Bahl AK. A phase II trial of cabazitaxel as second line chemotherapy in relapsed locally advanced and/or metastatic carcinoma of the penis. J Int Med Res. 2019 Oct;47(10):4664-4672.	Cabazitaxel is not likely to improve outcomes more than currents standards of care in the treatment of advanced penile cancer. We can move on and explore other candidate therapies. 17 patients were enrolled to reach this decision, which reflects efficient use of limited resources.	Designed, driven and delivered by the penile cancer subgroup.
Kelly JD, Tan WS, Porta N, Mostafid H, Huddart R, Protheroe A, Bogle R, Blazeby J, Palmer A, Cresswell J, Johnson M, Brough R, Madaan S, Andrews S, Cruickshank C, Burnett S, Maynard L, Hall E; BOXIT Investigators. BOXIT-A Randomised Phase III Placebo-controlled Trial Evaluating the Addition of Celecoxib to Standard Treatment of Transitional Cell	Celecoxib does not improve outcomes from low and intermediate risk NMIBC. It is unlikely that any other NSAID would differ, so no further trials need be done. We can move on and explore other candidate therapies. Establish a network of likeminded investigators.	Designed, driven and delivered by the predecessor Bladder CSG.

Carcinoma of the Bladder (CRUK/07/004). Eur Urol. 2019 Apr;75(4):593-601		
Mostafid AH, Porta N, Cresswell J, Griffiths TRL, Kelly JD, Penegar SR, Davenport K, McGrath JS, Campain N, Cooke P, Masood S, Knowles MA, Feber A, Knight A, Catto JWF, Lewis R, Hall E. CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs surgical management in low-risk non-muscle-invasive bladder cancer. BJU Int. 2020 Mar 3.	Proof of principle regarding chemo-ablation, laying the groundwork for future proof of concept studies. Response rates were insufficient to progress this particular agent to phase III. Establish a network of likeminded investigators.	Designed, driven and delivered by the predecessor Bladder CSG.
Huddart RA, Hall E, Lewis R, Porta N, Crundwell M, Jenkins PJ, Rawlings C, Tremlett J, Campani L, Hendron C, Hussain SA, James ND; BC2001 Investigators. Patient-reported Quality of Life Outcomes in Patients Treated for Muscle-invasive BladderCancer with Radiotherapy ± Chemotherapy in the BC2001 Phase III Randomised Controlled Trial. Eur Urol. 2020	BC2001 established a new standard of care. These data confirm that the therapeutic gain does not come at a significant cost regarding QoL. Affirms the current practice.	Active involvement of the group throughout development and delivery of the original trial and its subsequent analyses.

Group involvement with NICE appraisals

NICE appraisal	Appraisal outcome	Group involvement with NICE appraisal
Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. Technology appraisal guidance [TA581]	Remains within CDF	Evidence submitted via RCP Previously a group letter from renal members to explain the complexities of the health economic case was submitted to the committee.
Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]	Ongoing appraisal	Evidence submitted via RCP
Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]	Ongoing appraisal	Evidence submitted via RCP
Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]	Not supported, and removed from CDF	Evidence submitted via RCP
Pembrolizumab with chemotherapy for untreated metastatic urothelial cancer ID1545	Ongoing appraisal	Evidence submitted via RCP