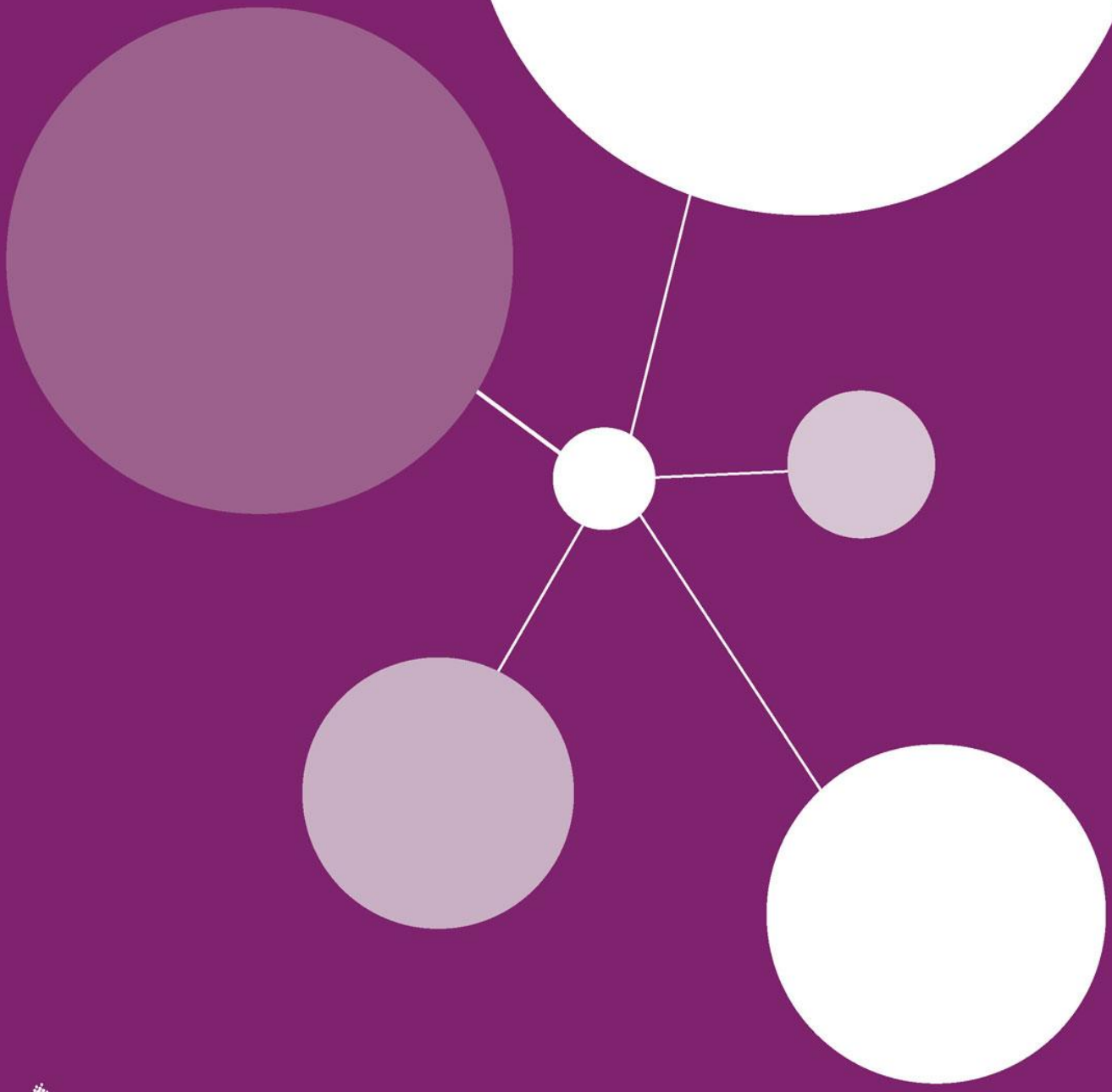
NCRI
National
Cancer
Research
Institute

NCRI Renal Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Renal Cancer CSG
Annual Report 2014/15

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

The incidence of renal cancer is increasing with 10,144 cases and 4252 deaths in the UK in 2011 and 2012 respectively (CRUK CancerStats). The development of new drugs for the treatment of advanced renal cancer in the last 10 years and the use of minimally invasive technologies to treat small tumours has changed the therapeutic landscape and the Renal CSG is responding to these developments. The main challenge for the group in 2014/2015 has been poor recruitment into interventional trials, particularly those involving surgery and as such, CARMENA was closed to recruitment in the UK in 2014. A similar trial, SURTIME, remains open to accrual despite withdrawal of CSG support in 2013 and recruitment remains very poor both in the UK and internationally. Recruitment to the CONSERVE trial was also poor. An ongoing challenge is the gap between the closure of the adjuvant SORCE trial in 2013 and the opening of the successor RAMPART trial.

The top three achievements for the group in the year were:

- Maintaining a high international profile for the CSG and the UK RCC academic community with oral presentations at ESMO 2014 and GU ASCO 2015 by Professors Tom Powles & Janet Brown and Dr James Larkin on academically-led portfolio trials COSAK, ZEBRA, STAR and E-PREDICT, respectively
- Successful strategy day December 2014
- Rejuvenation of the Surgical Subgroup under the leadership of Mr Grant Stewart

2. Structure of the Group

Professor Roz Banks (Basic Science), Mr Tim O'Brien (Surgery), Mr Naeem Soomro (Surgery) and Professor Tim Eisen (Medical Oncology) rotated off the group whilst Mr Christopher Blick (Surgery & CSG trainee), Dr Nav Vasudev, Dr Fiona Thistlethwaite and Dr Paul Nathan (Medical Oncology) joined the group in 2014/15. Currently the group has 2 consumer representatives, 1 representative from Kidney Cancer UK, 1 Radiologist, 4 Surgeons (including 1 trainee), 1 Statistician, 1 Clinical Oncologist, 1 Pathologist and 7 Medical Oncologists. Mr Stewart took over the chair of the Surgical Subgroup from Mr Soomro in 2014.

3. CSG & Subgroup strategies

Main CSG

Since 2005, the Renal CSG has designed a programme of clinical trials to answer the following questions:

- For tumours confined to the kidney, what is the most effective treatment?
- Following nephrectomy, in patients at significant risk of developing metastases, is there a role for adjuvant therapy?
- What is the role of cytoreductive nephrectomy in those presenting with metastatic disease?
- Can predictive biomarkers be found to tailor individual therapy?
- Can we gain an understanding of mechanisms of resistance to systemic therapy?
- Can more effective systemic treatments be developed for all histological subtypes?
- Can targeted systemic therapies be scheduled differently without detriment to efficacy but with improved quality of life for patients?

Surgical Subgroup (Chair, Mr Grant Stewart)

Background and challenges:

- Trials culture not embedded into renal cancer surgery culture
- Little engagement with renal cancer surgeons in UK
- Currently only 2 multicentre surgical trials on the portfolio (A-PREDICT and SURAB)
- There had not been any surgical subgroup meetings for at least the past 3 years
- The small renal mass trial CONSERVE, a RCT comparing partial nephrectomy and ablation, failed to meet the recruitment target of 60 patients (23 patients randomised)
- Closure of CARMENA in UK due to failure to recruit and continued poor recruitment into SURTIME. The failure of these key trials accentuated the urgent need for greater surgical input into UK renal cancer trials portfolio and this will best happen via the CSG

Achievements:

- Appointment of new Surgical Subgroup chair in September 2014 (Mr Grant Stewart, Edinburgh)
- Re-establishing the Surgical Subgroup. Following engagement with BAUS to establish 'key players' in UK renal cancer surgery, the surgical subgroup was repopulated (see Appendix 1 for details). The first subgroup meeting will be held in May 2015
- Appointing a Renal CSG Surgical Fellow
- Improving recruitment to A-PREDICT by direct liaison with study surgeons
- Opening the SURAB trial (PI – Naeem Soomro, Newcastle), feasibility study of randomisation of patients with small renal masses to observation or ablation. Lessons learnt from CONSERVE have been employed

Aims/strategy (see Appendix 2B for details):

- Establish reasons for failure of key surgery related renal cancer trials
- Understand attitudes of British renal cancer surgeons towards involvement in clinical research and any barriers that exist
- Establish the clinical questions that British urologists believe are important in renal cancer

- Determine the trials that British renal cancer surgeons believe can be realistically delivered in the UK
- Develop a cadre of energetic renal cancer surgeons to help deliver trials
- Fill the surgical gaps in the portfolio e.g. neoadjuvant, surgical and adjuvant studies

4. Task groups/Working parties

There are no task groups or working parties in the Renal CSG.

5. Patient recruitment summary for last 5 years

Recruitment into interventional and non-interventional trials in RCC has declined year on year from 2012 to 2015, reflecting largely the closure of the adjuvant SORCE trial and its translational component TRANSORCE in early 2013 and the fact that the follow-up study RAMPART has not yet opened to recruitment. The first line metastatic STAR trial is currently recruiting 15-20 patients per month at a large number of centres around the UK with a target of approximately 1000 patients. As of May 2015, just under 400 patients have been recruited. There is currently no 2nd line trial on the portfolio and no large well recruiting surgical study. Recruitment into the single arm phase 2 A-PREDICT and PAZ02 studies has been relatively slow but steady and both trials are approximately 50% recruited as of May 2015. The randomised phase II 2nd line ZEBRA study was closed to recruitment early on the recommendation of the IDMC in 2014 as a consequence of inferior efficacy in the experimental arm in comparison with the standard arm. In the Renal CSG portfolio, 8 trials closed to recruitment and 2 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	283	384	150	384	2.6	6.6
2011/2012	143	752	122	608	2.1	10.4

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	434	833	329	696	4.0	8.6
2013/2014	596	345	497	322	6.1	4.0
2014/2015	154	255	130	255	1.6	3.1

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

Links to the French Renal Cancer Group (via the Renal Cross Channel Group) continue under the Chairmanship of Grant Stewart from the UK side and discussions regarding opening RAMPART in France and the UK continue. At the last meeting of the group in Lyon in 2015 it was decided that Italian colleagues would also be invited to join the group. A joint analysis of outcomes from

patients with glandular (pancreatic, thyroid etc.) metastases was presented at ESMO 2014 and submitted for publication and an analysis of patients with metastatic chromophobe renal cancer (a rare histological subtype) will be presented at ASCO 2015. A number of other initiatives are under discussion. The French-led CARMENA trial has recruited reasonably well in France but poor UK recruitment led to the closure of the trial in the UK in 2014. Closer links with the Bladder CSG have been established given poor recruitment into trials in both tumour types and a joint road show is planned in Birmingham in May 2015. Links have been formed with the CLRN Urology Subspecialty Leads after a meeting in London in spring 2015 and it is hoped that this group can work effectively with the CSG in increasing recruitment into trials, helping to troubleshoot delivery issues and ensuring geographical equity of access for patients.

7. Funding applications in last year

The TRAPAZ trial has been designed rationally on the basis of preclinical work from the laboratory of Dr Andrew Reynolds at the Institute of Cancer Research where CSG Medical Oncologist Dr Vasudev undertook a period of post-doctoral research. The preclinical data showed that MEK inhibition can delay the acquisition of resistance to VEGF targeted therapy in RCC and as such the TRAPAZ trial is designed to test this hypothesis in the clinic. Support for the study was agreed with GSK (manufacturers of pazopanib and trametinib) in 2014 but this support was not confirmed after the subsequent GSK/Novartis merger. As such the development of the trial is on hold until such time as there is industry support. The CORE trial of SBRT for oligometastatic disease led by Dr Vincent Khoo originally included an RCC cohort but the Renal CSG did not feel that this was a feasible proposition and as such this cohort was removed from the study before CTAAC submission. The trial was subsequently funded by CTAAC in November 2014 with prostate, breast and NSCLC cohorts.

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
None			
November 2014			
None			
March 2015			
TRAPAZ: a randomised phase 2 study of pazopanib+/- trametinib in the first line treatment of RCC	Outline application	Dr Paul Nathan and Dr Nav Vasudev	application withdrawn because of re-prioritisation with GSK/Novartis after merger communicated to TRAPAZ team after CTAAC deadline

8. Collaborative partnership studies with industry

Collaboration with Pfizer on the A-PREDICT trial which opened in 2012 has been maintained and collaboration with GSK/Novartis on the PAZ02 trial continues. Discussions with a number of industry partners about the follow-up trial to SORCE, RAMPART, are ongoing. These include Pfizer, Argos, AZ and BMS. Professor Powles has secured agreement from AZ for a signal searching study combining MET inhibition with anti-PDL1 therapy in clear cell and papillary kidney cancer and Drs Glen and Vasudev are in discussion with a number of potential industry partners

including Eisai, Pfizer and AZ to try to set up a 'STAMPEDE-like' rolling 2nd line study. The main industry studies on the portfolio are registration anti-PD1 and anti-PD-L1 studies from BMS and Roche/Genentech which have been open at 5 to 10 centres in the UK in 2013-5. As such recruitment into these studies, most of which are in the 1st line metastatic setting, has not had a major impact on recruitment into the flagship STAR trial. It is anticipated that recruitment into these registration studies will complete by mid 2016 at the latest. Mr Stewart is at an advanced level of discussion with Pfizer to fund a 20 patient feasibility study of neoadjuvant axitinib in patients with RCC with renal vein or IVC venous tumour thrombus for 8 weeks prior to surgical resection.

9. Impact of CSG activities

The Renal CSG still awaits mature trial results. The adjuvant SORCE trial which closed to accrual in 2013 is potentially practice-changing but will not report until 2016 at the earliest. The STAR trial is also potentially practice-changing; recruitment is currently satisfactory (~40% recruited) but the trial is unlikely to close to recruitment before 2017. Molecular data from the E-PREDICT trial (Gerlinger et al NEJM 2012) has not changed clinical practice but has been conceptually influential in terms of understanding cancer biology as evidenced by over 2000 citations in the scientific literature as of May 2015. Current and previous CSG members played a significant role in the recent NICE approval of axitinib for the treatment of sunitinib-refractory metastatic disease.

10. Consumer involvement

Christy Watson

I joined the group in December 2014 and have attended 2 CSG meetings and the 5 Year Strategic Meeting. I have attended a few training courses organised by the NCRI to help me understand my role and the function of the organisation and its partners. The training also gave me an introduction to clinical trials and some of the terminology used.

Dr Larkin has agreed to be my mentor and is very approachable and supportive. We discuss regularly, via phone or email, what is happening within the Group and any action that I should take. If I have any concerns or questions he is my first point of contact.

I've been involved in writing to key sites that are not recruiting onto the STAR Trial to try and understand the barriers that are preventing them from opening the trial. I'll continue to follow this up. I will also be attending the Renal/Bladder Cancer Roadshow on May 12th and speaking at this event about my experience on a clinical trial, and about patient engagement. I have also put together a questionnaire so that we can evaluate the roadshow and capture feedback for future events.

I have suggested that a poster campaign would be an effective way to raise awareness about clinical trials and provide a sign post for patients who want more information about trials. I'm hoping that the posters may encourage patients to initiate a discussion with their clinician about trials and research. This is a project which I'll be working on in partnership with my fellow consumer members.

Pat Hanlon

I am a member of the trial management groups for the following studies: SORCE at the Medical Research Council, University College London; STAR at the Clinical Trials Research Unit, University of Leeds; SURAB at the Freeman Hospital, Newcastle-upon-Tyne; PAZ02 at the Queen Elizabeth Hospital, Birmingham; and HTA 11/107/07 at the University of Southampton. In addition I serve on the trial development group for the RAMPART study being developed by the Medial Research Council.

In my capacity as a Trustee of Kidney Cancer UK (KCUK), my main activity is campaigning for access to new drugs in the treatment of renal cell carcinoma: sunitinib and pazopanib in first line and axitinib and everolimus in second line. All 4 drugs are now recognised by the Cancer Drugs Fund and by the Scottish Medicines Consortium, but only the first three by the National Institute of Health and Clinical Excellence. It is expected that there will be a re-evaluation of everolimus by NICE, for which once again KCUK expects to be an official consultee.

Another major activity I am engaged in is the 'Be Clear on Cancer' publicity campaign launched by the Department Of Health. This has been highly successful and KCUK is urging that it be made into a regular annual event. The 'Blood in Pee' section has resulted in many patients being diagnosed earlier than they might otherwise have been.

Rose Woodward

My primary focus this year as a consumer representative on the Renal CSG has been to encourage the Group to consider how patients can be better involved in disseminating information about clinical trials and whether informed and active patients can improve the recruitment and retention of their fellow patients in renal cancer trials. I believe passionately that every patient should have the opportunity, if they wish, to be part of a clinical trial but this will only happen if patients have adequate information and if there is equitable access to trials across the Country.

To this end, I have scoped a "Patient Champion" project aimed at identifying and offering training to small teams of patients and carers within the 15 regional CRNs in England (we also plan to extend the programme to Scotland, Wales and Northern Ireland). We will help these teams to form relationships with CRN leads and speciality leads to improve the geographical spread of renal cancer trial sites. The teams will also provide information and support to patients locally to promote participation in trials via a new patient-run, patient funded website and a unique social networking site which will provide news and updates about research and clinical trials. With support from my scientific mentor Dr Fiona Thistlethwaite and our Chair, Dr Larkin, the CSG has also agreed to provide a patient friendly update of non-confidential Group activities following each CSG meeting.

I was also very pleased to be asked to serve on the newly formed Surgical Subgroup chaired by Mr Grant Stewart, and I am part of the Trial Steering Committee for the SURAB study.

11. Open meetings/annual trials days/strategy days

A strategy day facilitated by Professor Max Parmar was held in London in December 2014. This provided an opportunity to reflect on the current treatment landscape in kidney cancer, the progress of the CSG over recent years and to prioritise future areas of activity. We were very

grateful for the attendance and advice of a number of external colleagues such as Professor Johnathan Joffe, Mr Jim Paul, Mr David Nicol and Mr Richard Shaw. The main priorities identified for the next 2 years were: 1) Opening the RAMPART study as quickly as possible 2) Understanding the reasons for poor recruitment into surgical trials in the last 5 years and re-engaging with the RCC surgical community 3) Trying to ensure geographical equity of access to clinical trials for patients with RCC, particularly with respect to the STAR trial 4) Developing a rolling 2nd line metastatic 'STAMPEDE-like' trial 5) Developing a research programme in elderly, frail and unfit patients 6) Increasing links with the supportive/palliative care and psychosocial oncology/survivorship CSGs 7) Developing a UK-wide network of patient 'research champions'. Named members of the CSG have agreed to lead on each of these priorities.

In the light of poor recruitment nationally into RCC and bladder cancer trials in recent years, Dr Larkin and Dr Alison Birtle (Chair, Bladder CSG) reviewed accrual according to the LCRN networks in order to identify potentially productive areas for clinical trial 'road shows'. The West Midlands and Kent/Surrey/Sussex networks were felt to be the areas with greatest scope for improved recruitment and as such with the help of Dr Rik Bryan in Birmingham (Academic Urologist and Bladder CSG subgroup member) and Mr Hugh Mostafid in Guildford (Urologist and Bladder CSG member), road shows were organised in these areas in the Spring of 2015. Invitations were sent very widely to all those involved in treating RCC and bladder cancer as well as to LCRN teams. The response to invitations to the Guildford road show was so poor that the decision was taken to cancel it but the Birmingham road show will take place in May 2015.

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

The following questions have directed the Renal CSG in the development of studies; trials addressing these questions are inserted in parentheses:

- For tumours confined to the kidney what is the most effective surgical/minimally invasive treatment? (CONSERVE/SURAB)
- Following nephrectomy, in patients identified at risk of developing metastases is there a role for adjuvant therapy? (SORCE/RAMPART)
- Is there a role for cytoreductive nephrectomy in patients presenting with metastatic disease? (CARMENA/SURTIME)
- Can predictive biomarkers be found to tailor individual therapy? (A-PREDICT/Biomarkers study/SuMR/PANTHER/SCOTRRCC/EUROTARGET)
- Can we gain an understanding of mechanisms of resistance to systemic therapy? (A-PREDICT/SuMR/PANTHER)
- Can more effective systemic treatments be developed? (ZEBRA/COSAK)
- Can targeted systemic therapies be scheduled differently without detriment to efficacy but with improved quality of life for patients? (STAR)

Many of these studies are still recruiting although CARMENA, E-PREDICT, COSAK and ZEBRA are now closed to recruitment. The failure of CARMENA to recruit is discussed elsewhere in this report and the randomised phase 2 ZEBRA trial of the dual TORC inhibitor AZD2014 versus everolimus in VEGF refractory disease was stopped early for inferior efficacy in the experimental arm in 2014.

The Progress Review report in 2010 identified the need to focus more on translational research and this is being addressed with the ongoing Renal Biomarker Study, PREDICT, SCOTRRCC and EUROTARGET projects. The Progress Review Report in 2013 identified patchy recruitment as an issue and we hope that the planned road show and surgical initiatives will have some impact in this regard. Nevertheless there are some LCRNs where there is minimal or no recruitment into interventional academically-led portfolio studies such as STAR, PAZ02 and A-PREDICT, notably South Midlands/Thames Valley and the West of England. In this context, the CSG has made repeated attempts to understand the barriers to opening the STAR trial in Bristol and Oxford, including attempts to engage with the Urology Subspecialty Leads and letters sent from the consumer representatives to local investigators but at the time of writing no progress has been made in understanding the obstacles or indeed opening the trial at these centres. As such, patients with metastatic RCC that live in these areas do not have an opportunity to participate in this study, although notably the trial is open in Bath and Swindon for those patients prepared to travel within these networks after appropriate referral. We hope that the patient champion programme that the consumer representatives are putting together will help raise awareness of clinical trials amongst patients such that they ask to be referred to centres that are active in RCC research if they are being treated at an institution that is not research active.

13. Priorities and challenges for the forthcoming year

Priority: opening the adjuvant RAMPART trial as soon as possible

Prolonged negotiations with potential industry partners have delayed the development and opening of the RAMPART trial which has been under discussion since 2012. The predecessor trial, SORCE, closed to recruitment in early 2013 and RAMPART has been designed in conjunction with the MRC Clinical Trials Unit as a multi-arm multistage study (MAMS) allowing the opening of new trial arms during the lifetime of the trial. This design is particularly suitable for the adjuvant setting in RCC where there is a possibility of changing standards of care in the next 5 years as the first generation of adjuvant trials such as SORCE begin to report. One of the major questions for RAMPART had been whether VEGFR TKI therapy could be given at low doses for periods in excess of 12 months. At GU ASCO 2015 the first adjuvant VEGFR TKI trial of 12 months of sunitinib versus 12 months of sorafenib versus observation was reported as negative for the primary endpoint of disease free survival. As such the enthusiasm of our industry partners of including a VEGFR TKI arm in the RAMPART trial was significantly diminished and the current plan is to open RAMPART with 1 investigational arm of anti-PD1 or anti-PD-L1 therapy. Discussions with industry partners are at an advanced stage and we hope to have agreement in June 2015 with a CTAAC submission planned for July 2015.

Priority: opening a rolling 2nd line metastatic trial

The MAMS trials design has a number of advantages over traditional designs as discussed above and illustrated by the STAMPEDE trial in prostate cancer. Second line treatment for metastatic RCC has typically modest benefits with median progression free survival around 5 months whatever drug is used (generally axitinib or everolimus). Thus there is considerable scope to improve outcomes and a MAMS design would allow the rapid testing of promising agents and allow comparison with a standard of care such as axitinib. This could allow subsequent evaluation in the 1st line setting or the adjuvant setting in RAMPART. Second line RCC trials in general have recruited well in the UK in the last 2-3 years (ZEBRA, COSAK) and as such the CSG

feels that this is an area in which it can be competitive internationally. Possible agents for testing are anti-PD1/PD-L1 combinations, particularly with anti-CTLA or anti-VEGF.

Challenge: re-engaging with the British RCC Surgical community

Please see detailed comments elsewhere in this report.

14. Concluding remarks

The last year has seen further reductions in recruitment into clinical trials in RCC, particularly those with a surgical emphasis. Furthermore, the RAMPART trial still has not opened and there is significant geographical variation in trial recruitment, particularly within England. Despite these challenges, the CSG has maintained its international profile and held a successful strategy day and a clinical trial road show is planned. Engagement of our consumer representatives is excellent and we believe that our updated strategy contains the elements necessary to increase the number of trials in the portfolio, increase recruitment over the next 5 years and continue to deliver internationally competitive clinical research in kidney cancer.

15. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
A – Main CSG Strategy
B – Surgical Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Dr James Larkin (Renal CSG Chair)

Appendix 1

Membership of the Renal CSG

Name	Specialism	Location
Ms Caroline Bray	Statistician	Glasgow
Professor Janet Brown	Medical Oncologist	Leeds
Professor Stewart Fleming	Pathologist	Dundee
Dr Hilary Glen	Medical Oncologist	Glasgow
Professor Vicky Goh	Radiologist	London
Dr Pat Hanlon	Kidney Cancer UK	Birmingham
Dr Vincent Khoo	Clinical Oncologist	London
Dr James Larkin (Chair)	Medical Oncologist	London
Dr Paul Nathan	Medical Oncologist	Middlesex
Mr Grenville Oades	Surgeon	Glasgow
Professor Thomas Powles	Medical Oncologist	London
Mr Grant Stewart	Surgeon	Edinburgh
Mr Mark Sullivan	Surgeon	Oxford
Dr Fiona Thistlethwaite	Medical Oncologist	Manchester
Dr Naveen Vasudev	Medical Oncologist	Leeds
Mrs Christy Watson	Consumer	South Ayrshire
Mrs Rose Woodward	Consumer	Truro
Mr Christopher Blick*	Surgeon	Oxford

* denotes trainee

Membership of the Subgroups

Surgical Subgroup		
Name	**Specialism**	**Location**
Mrs Rose Woodward	Consumer	Truro
Mr Christopher Blick*	Surgeon	Oxford
Mr Steve Bromage	Surgeon	Manchester
Mr Jon Cartledge	Surgeon	Leeds
Mr Anurag Golash	Surgeon	Stafford
Mr Pieter Le Roux	Surgeon	London
Mr David Nicol	Surgeon	London
Mr Grenville Oades	Surgeon	Glasgow
Mr Tony Riddick	Surgeon	Cambridge
Mr Grant Stewart (Chair)	Surgeon	Edinburgh
Mr Mark Sullivan	Surgeon	Oxford

* denotes trainee

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

Updated Renal CSG Strategy after strategy meeting December 2014:

- Work in collaboration with others (Clinical Trials Units, NIHR, CRUK, LCRNs, other CSGs, industry, international groups, patient and consumer groups) to try to ensure a programme of clinical trials suitable for all patients with kidney cancer
- Understand and address the reasons for poor recruitment into surgical trials in the last 5 years and re-engage with the RCC surgical community
- Ensure geographical equity of access to clinical trials for patients with RCC
- Develop a research programme in elderly, frail and unfit patients and increase links with the supportive/palliative care and psychosocial oncology/survivorship CSGs
- Develop a UK-wide network of patient 'research champions'
- Develop and deliver a programme of clinical trials to answer the following questions:
  - For tumours confined to the kidney, what is the most effective treatment?
  - Following nephrectomy, in patients at significant risk of developing metastases, is there a role for adjuvant therapy?
  - Can predictive biomarkers be found to tailor individual therapy?
  - Can we gain an understanding of mechanisms of resistance to systemic therapy?
  - Can more effective systemic treatments be developed for all histological subtypes?
  - Can targeted systemic therapies be scheduled differently without detriment to efficacy but with improved quality of life for patients?

B – Surgical Subgroup Strategy

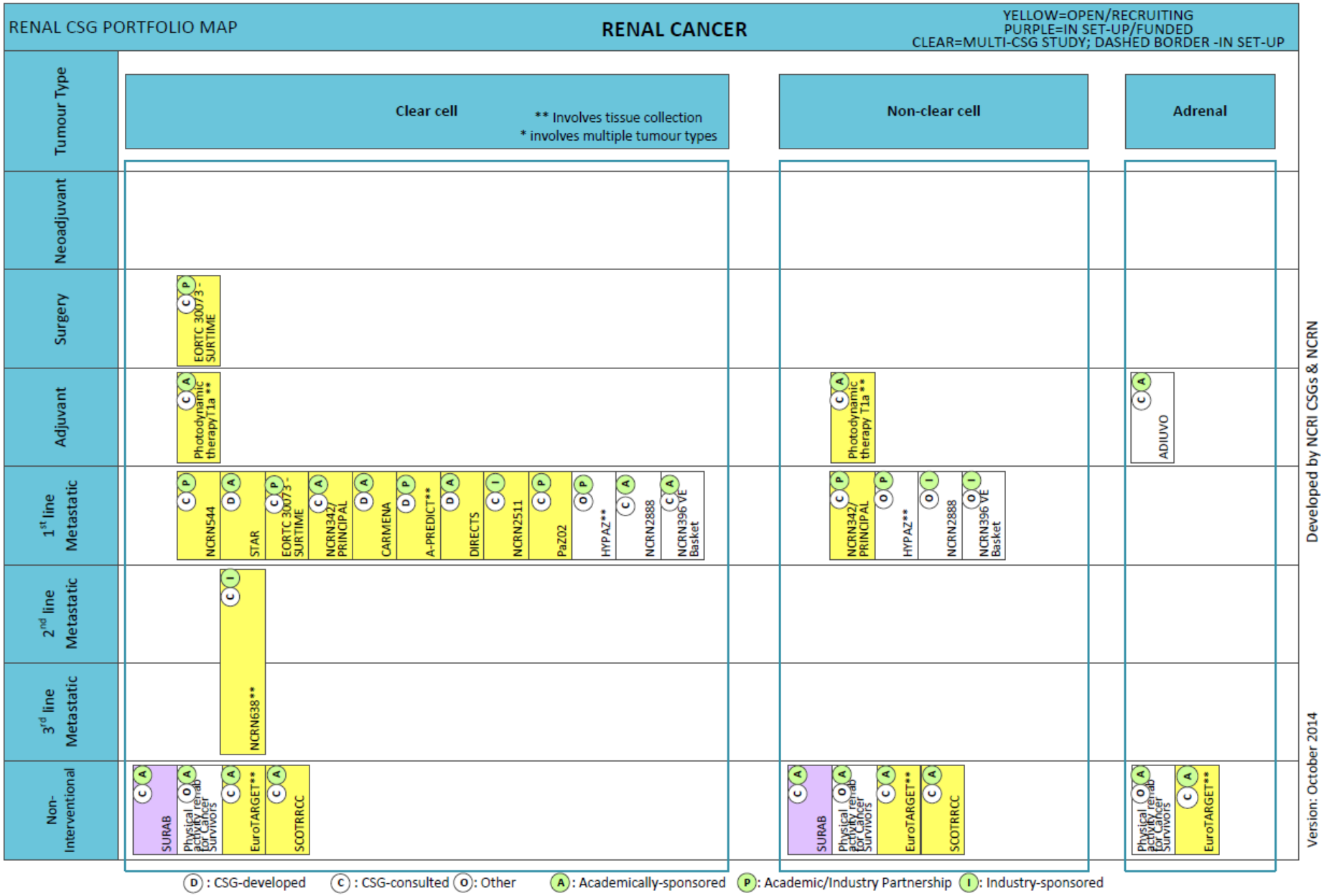
- Subgroup meetings planned as one face-to-face subgroup meeting/yr (travel and venue funded by NCRI) and one TC/yr. First meeting 28th May 2015. Next meeting will be a teleconference in November 2015.
- After assessment of barriers to energetic, keen individuals to trial recruitment determine which barriers can be overcome with assistance of key stakeholders i.e. NCRI, CRUK, local CRNs.
- Next set of surgical trials will be small phase II trials prior to any large scale study (or feasibility/internal pilot study as part of the main study).
- Launch NAXIVA, a feasibility study of neoadjuvant study of axitinib for 2 months prior to nephrectomy for patients with IVC venous tumour thrombus.
- Definitive small renal mass study following completion of SURAB and reporting of CONSERVE (CI for both is Naeem Soomro, Newcastle).
- Consider robotic partial nephrectomy study, as NHS England will not commission any new robotic partial nephrectomy centres.
- Full backing of development of RAMPART study with lymphadenectomy sub-randomisation as a feasibility component.
- Harness the energy of the Renal CSG Surgical Fellow. Planned activities are:
  - GAP analysis coordination
  - RAMPART as a learning model for workings of a CTU. Has already started interacting with MRC CTU. (Alastair Ritchie)
  - Writing review on adjuvant studies (with Grant Stewart, Tim Eisen and Alastair Ritchie)
  - Engaging with BAUS on clinical trial needs/issues
- Surgical input into Renal CSG roadshows
- Continued engagement with NCRI Surgical Taskforce (coordinated by Professor Richard Shaw), to allow learning from other surgical specialities and tap into the planned workshop which will benefit development of renal cancer surgical trials across the UK.
- Obtain greater engagement from BAUS in clinical trials, with support from them on our core activities, such as advertisement of trials and trial related events (to be done in collaboration with prostate and bladder CSG surgical subgroup chairs).
- Explore options for a urology specific surgical trials session/course at BAUS 2016 to highlight the issues and also to educate urologists (to be done in collaboration with prostate and bladder CSG surgical subgroup chairs).

Appendix 3

Portfolio maps

Renal Portfolio Map - Industry Studies Key

Acronym/Shortened Title	Full Title
NCRN342/PRINCIPAL	Pazopanib Observational Study (PRINCIPAL) - A prospective observational study to capture real world treatment patterns and determine treatment outcomes in patients with advanced or metastatic renal cell carcinoma (RCC) receiving pazopanib
NCRN358	A randomized, open-label, phase III study of BMS-936558 vs everolimus in subjects with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy
NCRN305	A PHASE II, MULTICENTER TRIAL OF PF-03856884 (CVX-060), A SELECTIVE ANGIOPOIETIN-2 (ANG-2) INHIBITOR IN COMBINATION WITH AXITINIB IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC RENAL CELL CARCINOMA
NCRN484/TAURUS	A phase II randomized, double-blind, crossover, controlled, multi-center, subject preference study of tivozanib hydrochloride vs sunitinib in the treatment of subjects with metastatic renal cell carcinoma
NCRN488	A multicentre, open-label, early stopping design, proof of concept study with tasquinimod in treating patients with advanced or metastatic hepatocellular, ovarian, renal cell and gastric carcinomas
NCRN544	ADAPT/An International Phase 3 Randomized Trial of Autologous Dendritic Cell Immunotherapy (AGS-003) Plus Standard Treatment of Advanced Renal Cell Carcinoma
NCRN638	A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy
NCRN - 2511	MPDL3280A +/- bevacizumab vs sunitinib in untreated advanced RCCA Phase II, Randomized study of MPDL3280A administered as monotherapy or in combination with bevacizumab versus sunitinib in patients with untreated advanced renal cell carcinoma


RENAL CSG PORTFOLIO MAP
RENAL CANCER
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
CLEAR=MULTI-CSG STUDY; DASHED BORDER -IN SET-UP
Tumour Type
Neoadjuvant
Surgery
Adjuvant
1st line Metastatic
2nd line Metastatic
3rd line Metastatic
Non-Interventional
Clear cell
** Involves tissue collection
* involves multiple tumour types
Non-clear cell
Adrenal
EORTC 30073 - SURTIME
Photodynamic therapy T1a **
NCRN544
STAR
EORTC 30073 - SURTIME
NCRN342/ PRINCIPAL
CARMENA
A-PREDICT**
DIRECTS
NCRN2511
PaZ02
HYPAZ**
NCRN2888
NCRN396 VE Basket
NCRN638**
ADIUVO
SURAB
Physical activity rehab for cancer survivors
EuroTARGET**
SCOTRRCC
(D) : CSG-developed
(C) : CSG-consulted
(O): Other
(A): Academically-sponsored
(P): Academic/Industry Partnership
(I): Industry-sponsored
Developed by NCRI CSGs & NCRN
Version: October 2014

Appendix 4

Publications in the reporting year

SCOTRRCC

G.D. Stewart, A.C.P. Riddick, , F. Rae, C. Marshall, L. MacLeod, F.C. O'Mahony, A. Laird, S.A. McNeill, K.M. O'Connor, M. O'Donnell, P. Fineron, D.B. McLaren, M. Aitchison, G. Oades, J. Hair, M. Seywright, B. Little, R. Nairn, G. Lamb, T. Macleod, I. Dunn, A. Ramsey, R. Campbell, S. Leung, L. McLornan, M. Rahilly, I. Wilson, A-M. Pollock, D.J. Harrison. Translational research will fail without surgical leadership: SCOTRRCC a successful surgeon-led Nationwide translational research infrastructure in renal cancer. *The Surgeon. Journal of The Royal Colleges of Surgeons of Edinburgh and Ireland*. In press 2015.

G.D. Stewart, F.C. O'Mahony, A. Laird, S. Rashid, S.A. Martin, L. Eory, A.L.R. Lubbock, J. Nanda, M. O'Donnell, A. Mackay, P. Mullen, S.A. McNeill, A.C.P. Riddick, M. Aitchison, D. Berney, A. Bex, I.M. Overton, D.J. Harrison, T. Powles. Carbonic anhydrase 9 expression increases with VEGF targeted therapy and is predictive of outcome in metastatic clear cell renal cancer. *European Urology.* 2014; 66: 956-963.

A-PREDICT

G.D. Stewart, D.J. Harrison, C. Swanton, R. Lewis, J. Bliss, J. Larkin, D.L. Nicol, on behalf of the A-PREDICT TMG. Multidisciplinary urological engagement in translational renal cancer research. *BJU International*. 2014; 114: 474–475.

Multidisciplinary urological engagement in translational renal cancer research.Stewart GD, Harrison DJ, Swanton C, Lewis R, Bliss J, Larkin J, Nicol DL; A-PREDICT TMG. BJU Int. 2014 Oct;114(4):474-5. doi: 10.1111/bju.12697. Epub 2014 Jul 28. PMID: 25146641

COMPARZ

Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013 Aug 22;369(8):722-31. doi: 10.1056/NEJMoa1303989

Appendix 5

Major international presentations in the reporting year

SCOTRRCC

G.D. Stewart, C. Van Neste, A. Meynert, C. Semple, F. O'Mahony, A. Laird, A. MacKay, G. Trooskens, W. Van Criekinge, T. De Meyer, T. Powles, D.J. Harrison. Effect of sunitinib therapy on intratumoural heterogeneity and differential expression of genetic mutations and DNA methylation in metastatic renal cell cancer. EAU 2015 Annual Meeting, Madrid, Spain. March 2015.

G.D. Stewart, C. Van Neste, A. Meynert, C. Semple, F. O'Mahony, A. Laird, A. MacKay, G. Trooskens, W. Van Criekinge, T. De Meyer, T. Powles, D.J. Harrison. Effect of sunitinib treatment on mutations and methylation in metastatic renal cancer. GU ASCO Meeting, Orlando, Florida, USA. March 2015.

A Laird, D. Sproul, G.D. Stewart, D.J. Harrison, R.R. Meehan. Prognostic DNA methylation marks in clear cell renal cell carcinoma. BAUS Section of Oncology 2014 Annual Meeting

Laird, D. Sproul, G.D. Stewart, D.J. Harrison, R.R. Meehan. DNA Methylation of NEFM is a potential prognostic marker in clear cell renal cell carcinoma. EAU 2014 Annual Meeting European Urology Supplements, Volume 13, Issue 1, April 2014, Page e293.

G.D. Stewart, A. Laird, F.C. O'Mahony, L. Eory, A.L.R. Lubbock, J. Nanda, M. O'Donnell, A. Mackay, P. Mullen, S.A. McNeill, A.C.P. Riddick, J. Peters, P. Patki, M. Aitchison, D. Berney, A. Bex, I.M. Overton, D.J. Harrison, T. Powles. The effect of anti-VEGF tyrosine kinase inhibitors on biomarkers and tumour heterogeneity in metastatic clear cell renal cancer. EAU 2014 Annual Meeting, European Urology Supplements, Volume 13, Issue 1, April 2014, Page e197

SUMR

G.D. Stewart, C. Van Neste, A. Meynert, C. Semple, F. O'Mahony, A. Laird, A. MacKay, G. Trooskens, W. Van Criekinge, T. De Meyer, T. Powles, D.J. Harrison. Effect of sunitinib therapy on intratumoural heterogeneity and differential expression of genetic mutations and DNA methylation in metastatic renal cell cancer. EAU 2015 Annual Meeting, Madrid, Spain. March 2015.

G.D. Stewart, C. Van Neste, A. Meynert, C. Semple, F. O'Mahony, A. Laird, A. MacKay, G. Trooskens, W. Van Criekinge, T. De Meyer, T. Powles, D.J. Harrison. Effect of sunitinib treatment on mutations and methylation in metastatic renal cancer. GU ASCO Meeting, Orlando, Florida, USA. March 2015.

A-PREDICT

R.A. Fisher, A. Rowan, M. Stares, M.F. Webster-Smith, R. Lewis, L.S. Kilburn, D. Nicol, G. Stewart, A. Michael, N. Vasudev, S. Hazell, S. Turaljic, L.M. Pickering, M.E. Gore, C. Snowdon, J.M. Bliss, C. Swanton, J.M.G. Larkin. A-PREDICT: A phase II study of axitinib in patients with metastatic renal cell cancer unsuitable for nephrectomy (CRUKE/11/061). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS4597). ASCO 2014, Chigaco, Illinois, USA. June 2014.

A-PREDICT: A phase II multicentre study of axitinib in patients with metastatic renal cell cancer unsuitable for nephrectomy (CRUKE/11/061). Poster presentation at National Cancer Research Institute Conference, Liverpool, November 2014

E-PREDICT

Larkin, J. Focus on (molecular) pathology from a medical oncologist, GU ASCO Orlando 2015

Larkin, J. Precision medicine in kidney cancer and clinical trial design, ESMO Madrid 2014

STAR

A randomised multi-stage phase II/III trial of standard first-line therapy (sunitinib or pazopanib) comparing temporary cessation with allowing continuation, in the treatment of locally advanced and/or metastatic renal cancer (STAR Trial), NCRI Cancer Conference, 3-5 Nov 2014, Liverpool

The trials and tribulations of setting up a real-time central radiological review within an academic UK multi-centre clinical trial, NCRI Cancer Conference, 3-5 Nov 2014, Liverpool

Brown, J. STAR update slides: A Randomised Multi-Stage Phase II/III Trial of Standard first-line therapy (sunitinib or pazopanib) Comparing Temporary Cessation with Allowing Continuation, in the treatment of locally advanced and/or metastatic Renal Cancer, British Urological Group (BUG) Meeting, 12 Sept 2014

Brown, J. A Randomised Multi-Stage Phase II/III Trial of Standard first-line therapy (sunitinib or pazopanib) Comparing Temporary Cessation with Allowing Continuation, in the treatment of locally advanced and/or metastatic Renal Cancer, ASCO GU Cancers Symposium, 28 Feb 2015