NCRI
National
Cancer
Research
Institute

NCRI Upper Gastrointestinal Cancer Clinical Studies Group

Annual Report 2017-18

Partners in cancer research

NCRI Upper Gastrointestinal Cancer CSG Annual Report 2017-18

1. Top 3 achievements in the reporting year

Achievement 1 **Cancer Research UK (CRUK) and other funding of Precision PANC project** This provides the pancreatic portfolio with a unifying, translationally driven study for advanced pancreatic, arguably the cancer of most unmet need in the CSG.
Achievement 2 **Presentation of the BILCAP data** This 13-year project has defined the standard of care for adjuvant therapy following curative resection for biliary tract cancer.
Achievement 3 **Publication of TACE 2** The first academically sponsored multicentre phase III trial in HCC in the UK. Provided definitive evidence that sorafenib does not improve outcome when combined with TACE.

2. Structure of the Group

The CSG thanks Professor John Primrose for his chairmanship over 7 years, additionally the following members: Mr Chris Hurt, Professor Juan Valle, Mr Trevor Cox, Dr Was Mansoor, Mrs Yvone Carse and trainees Dr Nigel Jamieson and Dr Saoirse Dolly. In the coming reporting year, the main CSG will pilot a change to comprise a small executive group, with the responsibilities of developing studies devolved to the subgroups. This change is supported by the NCRI and increased support for the expanded role of subgroups has been acknowledged.

3. CSG & Subgroup strategies

Main CSG

The last meeting of the whole CSG in its current form was held on 4 December 2017. A strategy day was held on 13 March 2018 and focussed on the recommendations of the quinquennial report from 2017. A formal strategic plan is being produced to be ratified at a meeting of the executive CSG. A draft version can be seen in Appendix 2A.

Hepatobiliary Subgroup (Chair, Mr Hassan Malik)

Develop links with hepatologists to support further epidemiological, surveillance and preventative studies in high risk population for HCC

The Subgroup in the past had consisted of medical oncologists as well as two hepatobiliary surgeons. Since taking over as chair, we have formalised links with HCC UK and Cholangiocarcinoma UK – both multidisciplinary groups that are affiliated to BASL. In addition, we have identified 4 academic hepatologists to join our Subgroup and have contacted the Primary Care CSG in order for the group to have the broadest expertise to develop epidemiological, surveillance or preventative studies, in collaboration with our external partners.

Build a platform through which a biomarker driven approach to advanced disease is investigated

Of the tumours within the remit of the subgroup, cholangiocarcinoma is the arena where a stratified medicine platform could be developed. The subgroup through Professor John Bridgewater and Professor Juan Valle, have worked with French collaborators to develop ABC10 (MOBILE) study. This is a precision medicine guided maintenance study in advanced biliary tract cancer, which will be submitted for a funding application end of 2018.

Develop a working party with other CSG stakeholders to investigate the development of developing an umbrella study

The Subgroup has been authorised to lead a time limited Working Party to establish whether an umbrella study could be developed in non-colorectal metastatic disease. We have invited representatives from Upper Gastrointestinal CSG, Pancreatic Subgroup, Neuroendocrine (NE Subgroup, Breast Cancer CSG, Skin Cancer CSG, Gynaecological CSG, Lung CSG, Bladder & Renal CSG, Prostate CSG, Supportive and Palliative Care CSG and Sarcoma CSG. Two initial meetings have taken place which has led to development of a preliminary study design. The aim of this working partly will be to develop the design further with a view to application for funding end of 2018/early 2019.

Neuroendocrine Subgroup (Chair, Professor Tim Meyer)

Increase proportion of academically sponsored trials

The UK has been successful in attracting and leading impactful commercial trials in neuroendocrine tumours; CLARINET, RADIANT-4, LUNA and NETTER-1. However, the development of high-quality, academically sponsored trials is a major priority for the NET Subgroup and several proposals are currently in evolution. Building on NET01, NET02 (CI Dr Mairéad McNamara) will evaluate nanoliposomal irinotecan (nal-IRI)/5-fluorouracil (5-FU) or docetaxel as second-line therapy in patients with progressive poorly differentiated extra-pulmonary NET/NEC in a multi-centre, randomised, open-label, phase II trial. The trial will open in 2018. A trial of checkpoint inhibition and chemotherapy has been developed through the Combinations Alliance with AstraZeneca, and a revised proposal has been invited (CI Dr Debashis Sarker). There is pressing need for a trial of adjuvant therapy following liver resection and this is being developed by Professor Andrea Frilling.

Strengthen links with translational research

Dr Chrissie Thirlwell, Chair of UK and Ireland Neuroendocrine Tumour Society (UKINETS) research committee now sits on the NET Subgroup forming a key strategic link. She leads the Neuroendocrine tumour (NET) Genomics England Clinical Interpretation Partnership (GeCIP) which is anticipated to inform strategies for stratified approaches in NET. Despite limited success in attracting translational research funding in the UK, several investigators have been awarded significant funding from the US-based Neuroendocrine Tumor Research Foundation; Tim Meyer (IMMUNET), Dr Chrissie Thirlwell (Causes of small intestinal NET), Dr Raj Srirajaskanthan (Development of ex-vivo models). These proposals will build international links and strengthen the biological knowledge base on which to develop further studies.

Develop clinical studies in other NET tumours where there is an unmet need

The main focus of clinical trials to date, has been pancreatic and midgut NETs. There is a significant unmet need for bronchial NETs, hind-gut NETs and well differentiated G3 NETs. The development of clinical trials in these areas will be encouraged. To facilitate developments in bronchial NETs, Professor Denis Talbot, member of the Lung Cancer CSG has also been appointed to the NET subgroup.

Oesophagogastric Subgroup (Chair, Dr Tom Crosby)

Support and encourage translational research to increase understanding of the factors that cause and drive Oesophagogastric (OG) cancer

The main focus of the OG Subgroup has been development of a proposal to CRUK regarding a stratified medicine approach to OG Cancer – Oelixir, and a proposal led by Professor Rebecca Fitzgerald will be put to a bespoke panel in September 2018.

The main components will be further developing the scientific collaboration established through OCCAMS, a molecular MDT and a menu of adaptive trials and a National Research Network of excellence.

The importance of a focused cohesive application running from discovery science through translation to genomically stratified clinical trials was recognised.

The three work packages to deliver this are:

- WP1: Patient recruitment, genomic analysis and oncogenic MDT
- WP2: Hypothesis Driven Stratification Research for new therapy options (includes clinical observational research and pre-clinical investigations)
- WP3: Menu of Adaptive Clinical Trials. The following trials might form this initial menu:

1. OElixir-01 – Neo-adjuvant: A phase Ib/II platform for Immuno-oncology and ATR inhibitor combinations in neoadjuvant chemo- and chemoradiotherapy
2. OElixir-02 - adjuvant: A randomised Phase II study of immunotherapy +/- adjuvant chemotherapy
3. OElixir-03a - relapsed: A randomised Phase II/III study of CDK4/6 inhibitor versus docetaxel/paclitaxel in advanced oesophageal adenocarcinoma progressing after platinum based chemotherapy
4. OElixir-03b - relapsed : A randomised Phase II study of EGFR antibody drug conjugate versus docetaxel/paclitaxel in EGFR FISH positive advanced oesophageal adenocarcinoma progressing after platinum based chemotherapy.4. SOLAR/OElixir -05 – advanced (currently open): A Phase II study of Olaparib in advanced oesophageal adenocarcinoma progressing after platinum based chemotherapy.

With an integrated prospective evaluation of ctDNA as a prognostic biomarker following surgical resection

Develop strategies to prevent OG cancer and new diagnostic techniques to facilitate an early diagnosis

The Oesophagogastric Subgroup have been very active in this area. Previously supporting Aspect, BOSS and BEST 1 and 2. Results from these are beginning to lead to chemo-prevention and diagnostic strategies.

BEST3:

The BEST3 Trial looks to incorporate the Cytosponge test into clinical practice. 80 practices across East Anglia, the North East and Hampshire are currently active within the trial with 45 practices either running or having finished Cytosponge™ clinics. 600 participants have consented so far to receive the Cytosponge™ test (with 5000 enrolled overall). 20 newly-trained nurses are now autonomous in delivering the test to patients. Patients are receiving confirmatory endoscopies following a positive Cytosponge™ result at over 10 active hospital sites. The first Cambridgeshire patients enrolled into the study in 2017 will reach the end of their study follow-up period in May 2018._10 CRN regions will be taking part in the trial until mid-2019. New areas opening in mid-2018 are East Midlands, Thames Valley, North Thames and Yorkshire and Humber.

Develop innovative new therapeutic strategies

This will be one of the primary outputs of the Oelixir programme based on developing in time a precision medicine approach to OG disease with surgical, radiotherapy and systemic therapy based treatments.

GoAdapt

Although definition of suboptimal response to pre-operative treatment varies, there is no standard adjuvant treatment for these patients - this adjuvant treatment trial looks to standardise adjuvant treatment in suboptimal responders. Tumour mutational burden (TMB) could be used as stratifier for post-operative treatment – those with higher TMB may be more sensitive to immunotherapy. ctDNA could be used as well - there is a plan to do a comparison and combination of existing and novel platforms involving various centres e.g. Oxford, Cambridge and Leicester.

PLATFORM

This is an umbrella, adaptive trial of maintenance treatment following first line treatment of OG adenocarcinoma.

- HER-2 negative patients (~80%) will be randomised in a 1:1:1:1 fashion between:
  - Surveillance only (Arm A1: current UK standard)
  - Maintenance capecitabine (Arm A2)
  - Maintenance MEDI4736 (Arm A3)
  - Maintenance Rucaparib (Arm A4)
- HER-2 positive patients (~20%) will be randomised in a 1:1 fashion between:
  - Maintenance single-agent trastuzumab (Arm B1: current UK standard)
  - Experimental arm: In development (Arm B2) NCRI OG Subgroup meeting April 2018

This trial is currently running in 40 centres, with 150 patients randomised.

SCOPE trials

The results of SCOPE 1 determined we should investigate the safe intensification of loco-regional treatment in terms of radiotherapy dose and investigate changing systemic therapy on the basis of an early PET scan being used as a biomarker for poor treatment response. This is the basis of SCOPE 2.

NeoSCOPE will inform the neo-adjuvant components of GoAdapt.

Pancreatic Subgroup (Chair, Dr Steven Falk)

Have a portfolio actively recruiting and in development with early diagnosis, staging, therapy and supportive care

Key trials include:

- ESPAC5F: a feasibility study in borderline resectable pancreas cancer. This study is recruiting slowly which is likely related to the complex protocol and the strict definition of "borderline resectable".
- PANasta: Cattell Warren versus Blumgart techniques of pancreatico-jejunostomy.
- SCALOP 2: chemo-radiation in locally advanced disease. Study is recruiting ahead of target and the dose finding phase is complete. This study will re-open in April/May 2017 and is recruiting ahead of time and target.
- ACELARATE: a study in patients not suitable for aggressive combination therapies open in 30 centres

Support and encourage translational research to increase understanding of the factors that cause and drive pancreas cancer

The focus now (is a stratified approach through the overarching Precision PANC initiative for which a total of £33 million funding has been approved. This is a biomarker discovery programme that will generate new trials based on tissue collection.

All major UK trials groups have agreed to provide tissue into this project and all trials developed will be peer reviewed through the Subgroup**.**

Develop innovative new therapeutic strategies

Pancreas cancer remains a difficult to treat disease where progress has been disappointingly slow. Novel targets and therapeutic strategies are urgently required. The overarching Precision PANC initiative offers the opportunity probably the only one in our professional careers using a tissue based approach to be able to facilitate novel developments.

4. Task groups/Working parties

Remit of Oligometastatic Disease Working Party

To develop a CSG cross-cutting umbrella study in oligometastases (non-colorectal cancers) with a proposed output of an outline funding application to CR UK in September 2018 or NIHR HTA August 2018. Co-Chairs: Mr Hassan Malik (Surgeon) & Professor Gareth Griffiths (Statistician). Led by the Upper Gastrointestinal CSG, including representation from other CSGs including: Lung, Breast, Prostate, Gynaecological, Sarcoma, Bladder & Renal, Skin (plus PPI, NCRI CTU, pathology). Timeline: 1 year (from October 2018).

Progress to date

1 Face-to-face meeting and 2 teleconferences with a further face-to-face and 4 teleconferences planned. Decisions to date:

- **Primaries to include** (i.e. Breast, Prostate, Renal and Lung not included at this time due to other trials/current evidence). Four groups included (ready now: Upper GI (Liver, pancreas, NET, oesophageal); and potentially joining later: Gynae, Sarcoma & Melanoma);
- **Definition of population/oligometastatic disease** (i.e. primary had radical treatment and three lesions in up to two sites, includes synchronous and metachronous);
- **Trial aim** (i.e. offer loco-regional therapy within the context of oligo-metastatic state, primary endpoint OS);
- **Treatment options** (loco-regional therapy including surgery; RT and/or ablation). With ongoing discussions on trial designs and inclusion of a registry study (e.g. biomarker driven precision trial including novel imaging, liquid biopsy miRNA).

5. Funding applications in last year

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)				
Study	**Application type**	**CI**	**Outcome**	**Level of CSG input**
May 2017				
Proportion of tumour in the pre-treatment diagnostic biopsy: a predictive and prognostic biomarker in patients with oesophageal cancer	Full application	Professor Heike Grabsch	Not supported	CSG supported
Multi-feature US for the assessment and clinical management of NAFLD and HCC: a proof of concept study	Full application	Professor Simon Taylor-Robinson	Not supported	
Neo-AEGIS - Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (MAGIC regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction	Full application (no-cost amendment)	Dr Shaun Preston	Not supported	CSG supported
November 2017				
Integrating hENT1 and DPD to stratify adjuvant chemotherapy in resected pancreatic cancer patients	Biomarker Project Award (Full Application)	Professor Daniel Palmer	Not Supported	
A phase Ib study of itacitinib, a JAK1 inhibitor, in advanced hepatocellular carcinoma	Early Phase & Feasibility Study	Dr Rohini Sharma	Not Supported	

	(Full Application)			
A study of perioperative immunotherapy with Durvalumab Tremelimumab in resectable HCC. CRUK AZ Combinations Alliance	CRUK AZ Combinations Alliance	Professor Tim Meyer	Invited to Full	Formally presented at Hepatobiliary Subgroup and modified according to feedback prior to submission to Clinical Research Committee (CRC). PPI reps form both Hepatobiliary and NET subgroup contributed.
Biomarker-oriented parallel cohort study of carboplatin/etoposide/durvalumab/tremelimumab as first-line treatment in patients with poorly differentiated extra-pulmonary neuroendocrine carcinoma	CRUK AZ Combinations Alliance	Dr Debashis Sarker and Dr Mairéad McNamara	Revision invited	Formally presented to NET Subgroup prior to presentation to the Combinations Alliance committee.
A multicentre, international, open-label, randomised, phase II/III trial of TG01/GM-CSF with gemcitabine plus capecitabine vs gemcitabine plus capecitabine alone as adjuvant treatment in patients with RAS-mutant resected adenocarcinoma of the pancreas	Late Phase Study (Outline)	Professor Daniel Palmer	Invited to Full	
Other committees				
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**
HUNTER: Hepatocellular Carcinoma Expediter Network	CRUK Accelerator	Helen Reeves	Funded	Members of the Hepatobiliary Subgroup are work-package leads.

6. Consumer involvement

Philip Bell

Dr Philip Bell (non-medical doctorate) joined the group in July 2016 and has played an active role at CSG meetings, including giving a presentation on PPI to the group at the Strategy Day in March. Philip also sits on several cancer oversight committees for non-upper GI research projects such as PATHOS, RE-AKT and CreSt 2. He is also Vice Chair of the Cancer UK Clinical Trials Unit Patient and Public Involvement Group at Liverpool University from where he reflects the thoughts to the CSG. At present, we have only one consumer representative on the Group. The second consumer position is currently being advertised by the NCRI and it is hoped that this vacancy will soon be filled.

7. Priorities and challenges for the forthcoming year

Priority 1 Focus on expanding academic portfolio, primarily stratified cross-cutting study design attractive to funders.
Priority 2 Incorporation of translational objectives as fundamental to study design
Priority 3 Support and enable challenging innovative programmes e.g. Precision PANC through establishment of staff infrastructure across UK
Challenge 1 Adaptation of study design to translational and/or cross cutting novel designs
Challenge 2 Establish translational infrastructure in context of cash-strapped NHS
Challenge 3 Maintain research community beyond academic centres

8. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Hepatobiliary Subgroup Strategy
- C – Neuroendocrine Subgroup Strategy
- D – Oesophagogastric Subgroup Strategy
- E – Pancreatic Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 – Top 5 publications in reporting year

Appendix 5 – Recruitment to the NIHR portfolio in the reporting year

Appendix 6 – QQR feedback

Professor John Bridgewater (Upper Gastrointestinal Cancer CSG Chair)

Appendix 1

Membership of the Upper Gastrointestinal Cancer CSG

Name	Specialism	Location
Dr Saoirse Dolly*	Clinical Fellow	London
Dr Yuk Ting Ma	Clinical Lecturer	Birmingham
Dr Tom Crosby	Clinical Oncologist	Cardiff
Dr Stephen Falk	Clinical Oncologist	Bristol
Dr Maria Hawkins	Clinical Oncologist	Oxford
Dr Somnath Mukherjee	Clinical Oncologist	Oxford
Professor Tim Underwood	Clinical Scientist	Southampton
Dr Philip Bell	Consumer	Amlwch
Dr Bristi Basu	Medical Oncologist	Cambridge
Professor John Bridgewater (Chair)	Medical Oncologist	London
Professor Ruth Langley	Medical Oncologist	London
Professor Tim Meyer	Medical Oncologist	London
Professor Daniel Palmer	Medical Oncologist	Liverpool
Professor Russell Petty	Medical Oncologist	Aberdeen
Dr Paul Ross	Medical Oncologist	London
Dr Richard Turkington	Medical Oncologist	Belfast
Mrs Teresa Lockett	NIHR Research Delivery Manager	Oxford
Dr Gordon Hutchins	Pathologist	Leeds
Mr Richard Fox	Statistician	Birmingham
Professor Hugh Barr	Surgeon	Gloucester
Professor Andrew Biankin	Surgeon	Glasgow
Professor Paula Ghaneh	Surgeon	Liverpool
Mr Nigel Jamieson*	Surgeon	Glasgow
Mr Hassan Malik	Surgeon	Liverpool

* denotes trainee member

Membership of the Subgroups

Hepatobiliary Subgroup		
Name	**Specialism**	**Location**
Mrs Helen Morement	AMMF Chair of Trustees	London
Dr Saoirse Dolly*	Clinical Fellow	London
Dr Maria Hawkins	Clinical Oncologist	Oxford
Mr John Symons	Consumer	Newbury
Professor Helen Reeves	Gastroenterologist	Newcastle
Dr Bristi Basu**	Medical Oncologist	Cambridge
Dr John Bridgewater	Medical Oncologist	London
Dr Mairead Mcnamara**	Medical Oncologist	Manchester
Dr Tim Meyer	Medical Oncologist	London
Professor Daniel Palmer	Medical Oncologist	Liverpool
Mr Paul Ross	Medical Oncologist	London
Professor Juan Valle	Medical Oncologist	Manchester
Dr Harpreet Wasan	Medical Oncologist	London
Ms Pam O'Donoghue	Nurse	London
Dr Tim Kendall	Pathologist	Edinburgh
Dr Andre Lopes	Statistician	London
Dr John Primrose	Surgeon	Southampton
Mr Hassan Malik (Chair)	Surgeon	Liverpool

Neuroendocrine Subgroup		
Name	**Specialism**	**Location**
Ms Cathy Bouvier**	Consumer	Coventry
Ms Lindsey Devlin**	Consumer	Coventry
Paul Coffey **	Consumer	Coventry
Professor Martyn Caplin**	Gastroenterologist	London
Dr Jonathan Wadsley	Clinical Oncologist	Sheffield
Professor Nick Reed	Clinical Oncologist	Glasgow
Professor Ashley Grossman	Endocrinologist	London
Dr Alia Munir	Endocrinologist	Sheffield
Professor Mark Pritchard	Gastroenterologist	Liverpool
Dr John Ramage	Gastroenterologist	Hampshire
Dr Mohid Khan	Gastroenterologist	Cardiff
Dr Wasat Mansoor	Medical Oncologist	Manchester
Dr Mairead Mcnamara	Medical Oncologist	Manchester
Professor Tim Meyer (Chair)	Medical Oncologist	London
Dr Debashis Sarker**	Medical Oncologist	London
Professor Juan Valle	Medical Oncologist	Manchester
Dr Christina Thirlwell**	Medical Oncologist	London
Professor Denis Talbot	Medical Oncologist	Oxford
Dr Prakash Manoharan	Radiologist	Manchester
Professor Andrea Frilling**	Surgeon	London
Mr Neil Pearce	Surgeon	Southampton

Oesophagogastric Subgroup		
Name	**Specialism**	**Location**
Dr Tom Crosby (Chair)	Clinical Oncologist	Cardiff
Dr Somnath Mukherjee	Clinical Oncologist	Oxford
Mr David Chuter**	Consumer	Bognor Regis
Professor Heike Grabsch**	Histopathologist	Leeds
Professor David Cunningham	Medical Oncologist	London
Professor Jeff Evans	Medical Oncologist	Glasgow
Dr Hugo Ford	Medical Oncologist	Cambridge
Professor Janusz Jankowski	Medical Oncologist	Warwick
Dr Ruth Langley	Medical Oncologist	London
Dr Naureen Starling	Medical Oncologist	London
Professor Anne Thomas	Medical Oncologist	Leicester
Professor Gareth Griffiths**	Professor of Clinical Trials	Southampton
Professor Jane Blazeby	Surgeon	Bristol
Mr William Allum	Surgeon	London
Professor Robert Mason	Surgeon	London
Mr Shaun Preston**	Surgeon	Surrey
Professor Tim Underwood	Surgeon	Southampton

Pancreatic Subgroup		
Name	**Specialism**	**Location**
Dr Nigel Jamieson*	Clinical Lecturer	Glasgow
Dr Stephen Falk (Chair)	Clinical Oncologist	Bristol
Dr Somnath Mukherjee	Clinical Oncologist	Oxford
Ms Leanne Reynolds**	Head of Research, Pancreatic Cancer UK	London
Professor John Bridgewater	Medical Oncologist	London
Dr Pippa Corrie	Medical Oncologist	Cambridge
Professor Jeff Evans	Medical Oncologist	Glasgow
Professor Daniel Palmer	Medical Oncologist	Liverpool
Dr David Propper	Medical Oncologist	London
Professor Juan Valle	Medical Oncologist	Manchester
Dr Karin Oien	Pathologist	Glasgow
Trevor Cox	Statistician	Liverpool
Professor Paula Ghaneh	Surgeon	Liverpool
Professor John Primrose	Surgeon	Southampton
Professor Andrew Biankin	Surgeon	Glasgow

* denotes trainee member

**denotes non-core member

Appendix 2

A – Main CSG Strategy

The NCRI CSG is a recognised international authority in the research of UGI cancers. The overall strategic aim is to improve outcomes for patients with UGI malignancies through practice changing clinical and translational research.

The Group strategy was revised based on the Upper GI Quinquennial Review (QQR) on 24 April 2017 and modified following the Strategy Day held on Tuesday 13 March 2018:

Strategic aims

In order to continue to continue being internationally competitive the CSG strategic aims need:

1 Stratified molecular studies to exploit the expanding molecular knowledge base

2 Increased diversification to include more studies in parallel and related specialities such as surgery, radiotherapy, imaging and supportive care.

3 Exploit our relationships with the oncology community in trial design and conduct.

More detailed subgroup strategy to address these overall aims are given:

1. The subgroup structure was re-examined. It was widely agreed that with the advent of CTRad that radiotherapy should be embedded in the other subgroups and a relationship established with CTRad.
2. It was agreed that the Screening and Prevention Subgroup, which dealt only with Barrett's Oesophagus, was not appropriate and the suggestion was a group be formed which included prevention, screening, early diagnosis and imaging. Subsequently, however, the NCRI review of CSGs and Subgroups set an absolute maximum of four Subgroups and it was subsequently agreed that these areas would be embedded in the four remaining subgroups and a relationship established with the cross cutting Prevention, Screening and Early Diagnosis Advisory Group which has been set up across all CSGs.
3. The four Subgroups (oesophagogastric, pancreatic, hepatobiliary and neuroendocrine tumours) should remain in their present form but the membership and chair arrangements should conform to the new NCRI review proposals with a strict tenure of membership.
4. The membership of the subgroups would be reviewed and it was agreed that a statistician should sit on each subgroup.
5. CUP should be included within the Hepatobiliary Subgroup.
6. The Group felt that GIST, which sat with the Sarcoma CSG, should move to the Upper GI CSG on the basis that 1) GIST was not a sarcoma and 2) in terms of the clinical management it involved principally the Upper GI MDT. The Chair agreed to take this to the NCRI Directors.
7. New trial methodologies were discussed. It was accepted that very large phase III trials using a single chemotherapy schedule in unselected patients was probably in the past and that the future would be dominated by adaptive and biomarker driven trial designs.

8. Surgical trials were discussed. Accepting the problems with recruitment, it was agreed that it was appropriate to try to develop more high-quality trials in surgical methodologies.
9. Arrangements for the development of radiotherapy trials were discussed and it was agreed that the Group should work closely with CTRad to develop high quality radiotherapy proposals.
10. A major national strategy was to encourage and develop industry studies and the advantages of an AZ collaboration was discussed. It was agreed the Group would work to increase collaboration with industry trials.
11. The Group also considered various novel trial ideas which would be developed through the subgroups subsequently.

B –Hepatobiliary Subgroup Strategy

- Oligometastatic project
    - Following feedback from the QQR report, the Subgroup has set up a time limited working party with other CSG stakeholders to investigate the possibility of developing an umbrella study in this area.
- HCC: Following feedback from QQR, we will formally contact the UK HCC consortium to look at developing closer links with hepatologists and the CSG. This may enable us to support further epidemiological, surveillance and preventative studies in high risk population for HCC.
- Cholangiocarcinoma: Following on from the success of ABC studies, the Subgroup is keen to build a platform through which a biomarker driven approach to advanced disease could be investigated. If successful, such an approach could be applied to the adjuvant setting following completion of the ACTICCA1 study.

C – Neuroendocrine Subgroup Strategy

To improve outcomes for patients with NETs through clinical and translational research, built on a coordinated infrastructure for these rare tumours.

Strategy

Increase proportion of academically sponsored trials

The UK has been successful in attracting and leading impactful commercial trials in neuroendocrine tumours; CLARINET, RADIANT-4, LUNA and NETTER-1. However, the development of high-quality, academically sponsored trials is a major priority for the NET Sub-group and several proposals are currently in evolution. Building on NET01, NET02 (CI Mairéad McNamara) will evaluated nanoliposomal irinotecan (nal-IRI)/5-fluorouracil (5-FU) or docetaxel as second-line therapy in patients with progressive poorly differentiated extra-pulmonary NET/NEC in a multi-centre, randomised, open-label, phase II trial. The trial will open in 2018. A trial of checkpoint inhibition and chemotherapy has been developed through the Combinations Alliance with AstraZeneca, and a revised proposal has been invited (CI Debashis Sarker). There is pressing need for a trial of adjuvant therapy following liver resection and this is being developed by Andrea Frilling.

Strengthen links with translational research

Dr Chrissie Thirlwell, chair if UKINETS research committee now sits on the NET sub-group forming a key strategic link. She leads the NET GCIP which is anticipated to inform strategies for stratified approaches in NET. Despite limited success in attracting translational research funding in the UK, several investigators have been awarded significant funding from the US-based Neuroendocrine Tumor Research Foundation; Tim Meyer (IMMUNET), Chrissie Thirlwell (Causes of small intestinal NET), Raj Srirajaskanthan (Development of ex-vivo models). These proposals will build international links and strengthen the biological knowledge base on which to develop further studies.

Develop clinical studies in other NET tumours where there is an unmet need

The main focus of clinical trials to date, has been pancreatic and midgut NETs. There is a significant unmet need for bronchial NETs, hind-gut NETs and well differentiated G3 NETs. The development of clinical trials in these areas will be encouraged. To facilitate developments in bronchial NETs, Denis Talbot from the lung CSG has also been appointed to the NET subgroup. Quality of life studies will remain important John Ramage will build on a well-established track record in this area.

Given the rarity of these tumours, international links will remain key and strong links with the European Neuroendocrine Tumour Society maintained and developed.

D – Oesophagogastric Subgroup Strategy (2014 – 2018)

Aim

The Oesophagogastric Subgroup aims to improve outcomes for patients with OG cancer through progressive clinical trials and cutting edge translational research.

Strategy

The strategy of the Subgroup is to ensure that the OG trial portfolio provides comprehensive coverage of all aspects of OG cancer and achieves a balance between translational and clinical research. In particular, we will:

- Continue to support and encourage translational research to increase understanding of the factors that cause and drive OG cancer.
- Continue to develop strategies to prevent OG cancer and new diagnostic techniques to facilitate an early diagnosis.
- Continue to develop innovative new therapeutic strategies. This includes:
    - Investigating the role of immunotherapy in OG cancer and how it may be integrated into the paradigm for early and advanced disease, including possible combinations with radiotherapy, chemotherapy or targeted agents and biomarker selection.
    - Investigating novel therapies, new surgical techniques and advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT).
    - Developing and refining therapeutic strategies for all stages of disease, including neoadjuvant therapy, surgery/local therapies and adjuvant therapy for localised disease and multiple lines of treatment for advanced disease.
    - Developing trials that focus on common challenges in the management of OG cancer, including elderly patients, with an emphasis on research that can be translated into meaningful outcomes for patients.
    - Developing an evidence base for OG cancer to inform decision-making and health policy.

To deliver these priorities we will:

- Encourage collaborative approaches, seeking to increase both national and international partnerships to facilitate rapid study recruitment and cutting edge translational research. This includes supporting the establishment of national and international multi-centre trials, including trials with adaptive designs.
- Encourage industry partnerships, seeking to facilitate the rapid development of trials investigating new therapeutic agents.
- Continue to support and develop the best researchers, at all stages of their careers, by encouraging submission of trial proposals for discussion and feedback from the OG Subgroup.
- Assist with grant funding applications by providing a forum for peer-review and discussion of trial proposals, and letters outlining support for important new studies.
- Discuss areas of unmet need in cancer research, to enable trials to be developed to address major therapeutic challenges and any gaps in the portfolio.

E – Pancreatic Subgroup Strategy (2014-2018)

Aim

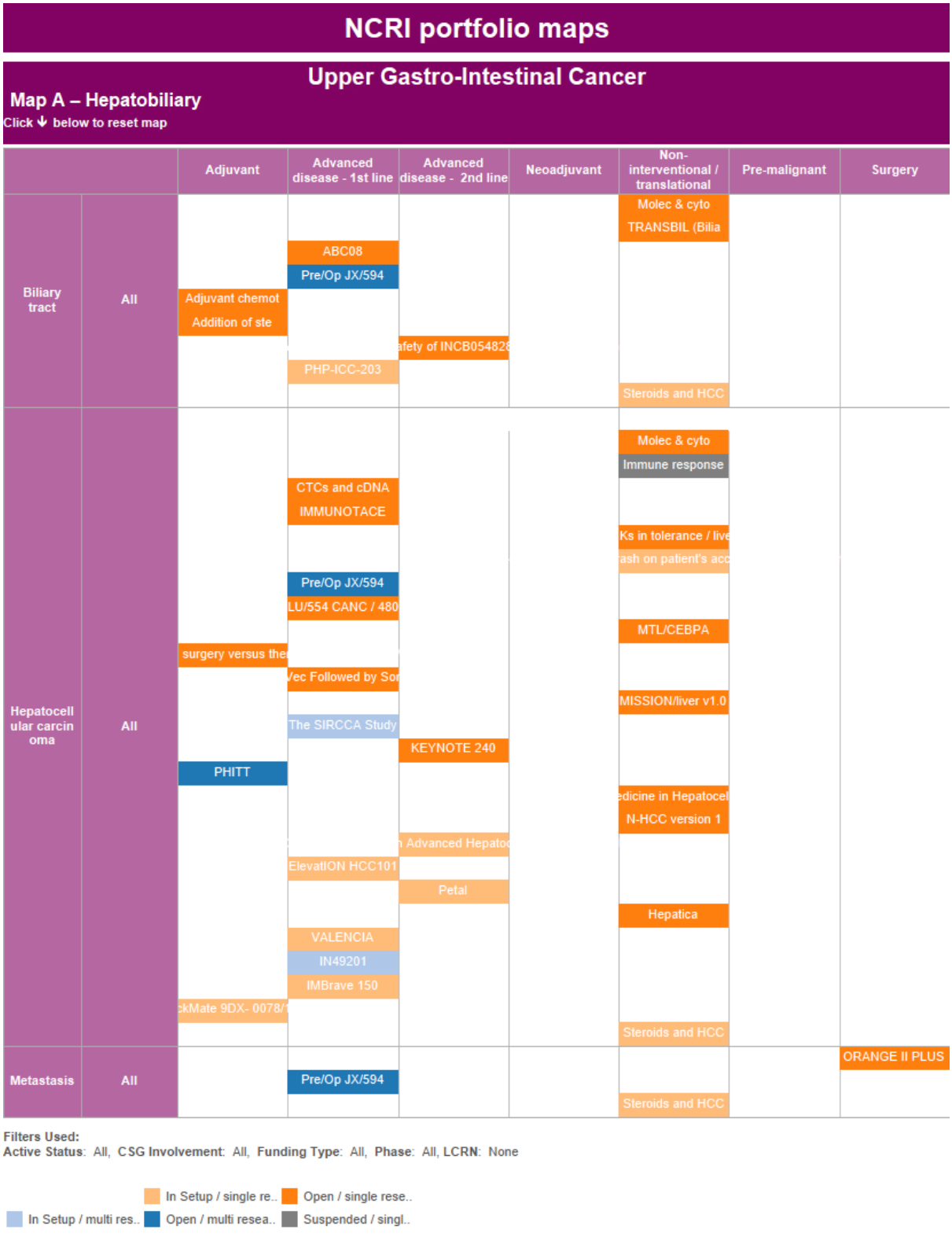
The Pancreatic Subgroup aims to improve outcomes for patients through a broad range of clinical trials encompassing all relevant clinical scenarios with cutting edge translational research.

Strategy

- To have a portfolio actively recruiting and in development within early diagnosis, staging, therapy and supportive care.
- Continue to support and encourage translational research to increase understanding of the factors that cause and drive pancreas cancer.
- Continue to develop innovative new therapeutic strategies. This includes:
    - Investigating novel targeted therapies, immunotherapy, new surgical techniques and advanced radiotherapy techniques such as intensity-modulated radiotherapy (IMRT).
    - Developing and refining therapeutic strategies for all stages of disease, including neoadjuvant therapy, surgery/local therapies and adjuvant therapy for localised disease and multiple lines of treatment for advanced disease.
    - Developing trials that focus on common challenges in the management of pancreas cancer, including symptoms such as cachexia.
    - Developing an evidence base for the molecular biology of pancreas cancer to inform decision-making and health policy.

Appendix 3

Portfolio maps



NCRI portfolio maps

Upper Gastro-Intestinal Cancer

Map B – Neuroendocrine

Click ↓ below to reset map

		Adjuvant	Advanced disease - 1st line	Neoadjuvant	Surgery	Symptom control / non-interventional / translational
Intestines	High grade (g3)		Axitinib in progressive COMPETE ClarIDHy			Target NET
	Low grade (g1/g2)		ClarIDHy			DIB/NET Study Target NET
Lung & other	High grade (g3)		SPINET Axitinib in progressive			Target NET
	Low grade (g1/g2)		SPINET			[18F]/FET/ßAG/TOCA IMMUNET Target NET
Pancreas	High grade (g3)		PDR001 in Neuroendocrine Tumours COMPETE CANC 5712	kinase inhibitor plus BSC EORTC QoL Module for		Target NET
	Low grade (g1/g2)	Pancreatic Endocrine	SEQTOR REMINET PDR001 in Neuroendocrine Tumours CANC 5712			[18F]/FET/ßAG/TOCA Target NET

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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NCRI portfolio maps

Upper Gastro-Intestinal Cancer

Map C – Oesophageal, junctional tumours (type I/II)

Click ↓ below to reset map

		Adjuvant	Advanced disease - 1st line	Advanced disease - 2nd line	Neoadjuvant	Non-interventional / translational	Pre-malignant	Surgery
Adenocarcinoma	All	Chopin Add/Aspirin Neo/AEGIS umab in gastric and a with Chemo (XP/F	Chopin ROCS isplatin+5-Fluoroura - 4472 (KEYNOTE ti-part, Phase 1/2a s ICONIC lacebo with chemo ECDMGC IN49201	Chopin ZD3965 in adv canc masitinib vs sunitinib 8 (MK-3475 in Gast table/Metastatic Es	Chopin Neo/AEGIS	Chopin OCCAMS: Multice RTL Advanced St RI For Staging Oes ERE Breathe : Vers CALIBRATION	Non/invasive diagn. GI precursor lesion CM5 ELISA test for	Chopin LITE Study Neo/AEGIS
Barrett's oesophagus	All		Pre/Op JX/594 LUD2015/005 ombination Therapy	ZD3965 in adv canc masitinib vs sunitinib		Molec & cyto MIMOSA Barrett's Epigenome omputer Aid for ass Identifying Pro n oesophageal/gast endomicroscopy in	RECaD Chopin Trimodal Imagin BEST2 Non/invasive diagn. GI precursor lesion OESophagus Trial 3	LITE Study mally invasive or op
Squamous cell carcinoma	All	Add/Aspirin	ROCS SCOPE 2 lacebo with chemo ECDMGC			PLATFORM mous cell CARcino RI For Staging Oes	Non/invasive diagn. CM5 ELISA test for	LITE Study

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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NCRI portfolio maps

Upper Gastro-Intestinal Cancer

Map D – Stomach, junctional tumours (type II/III)

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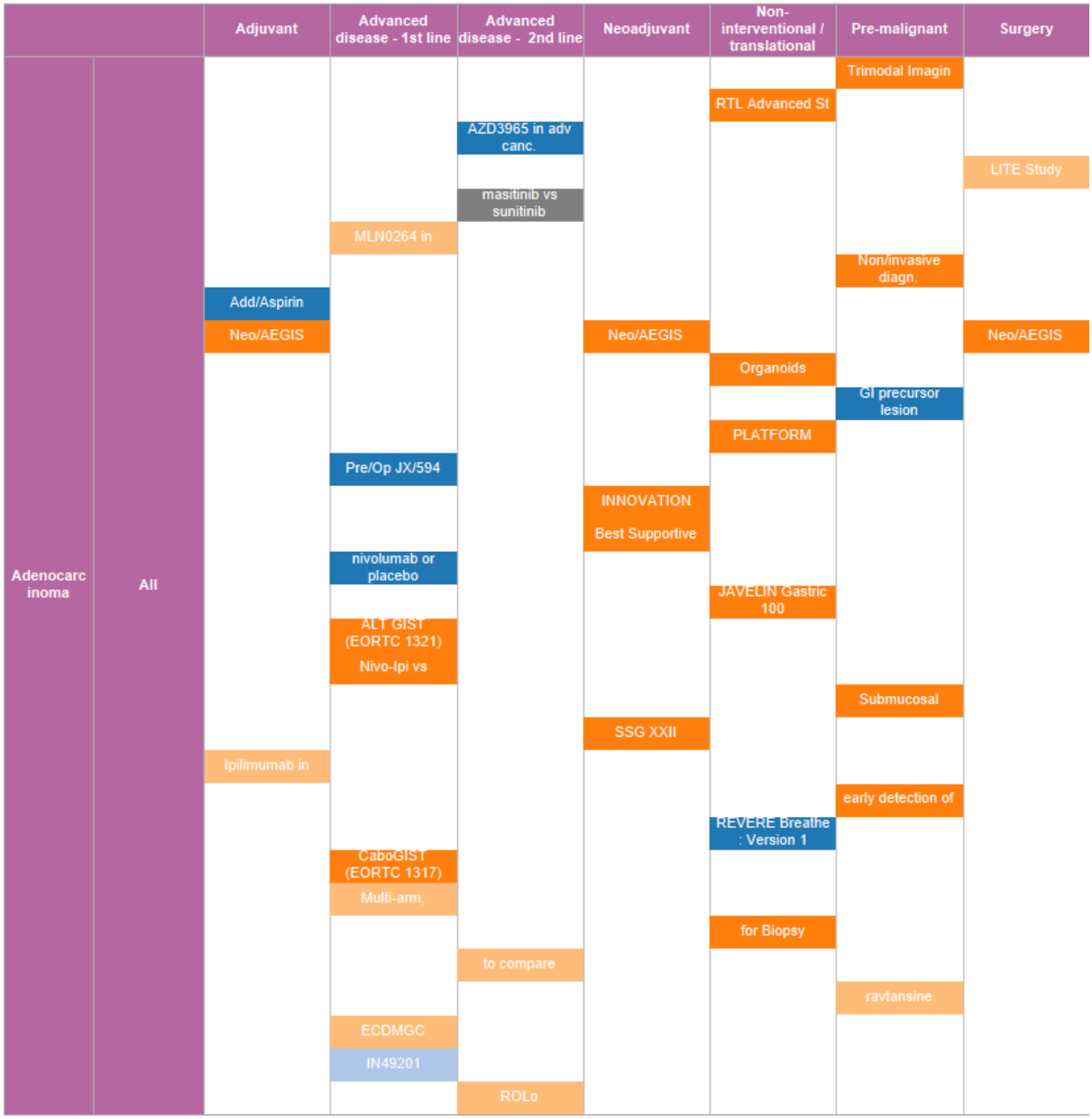

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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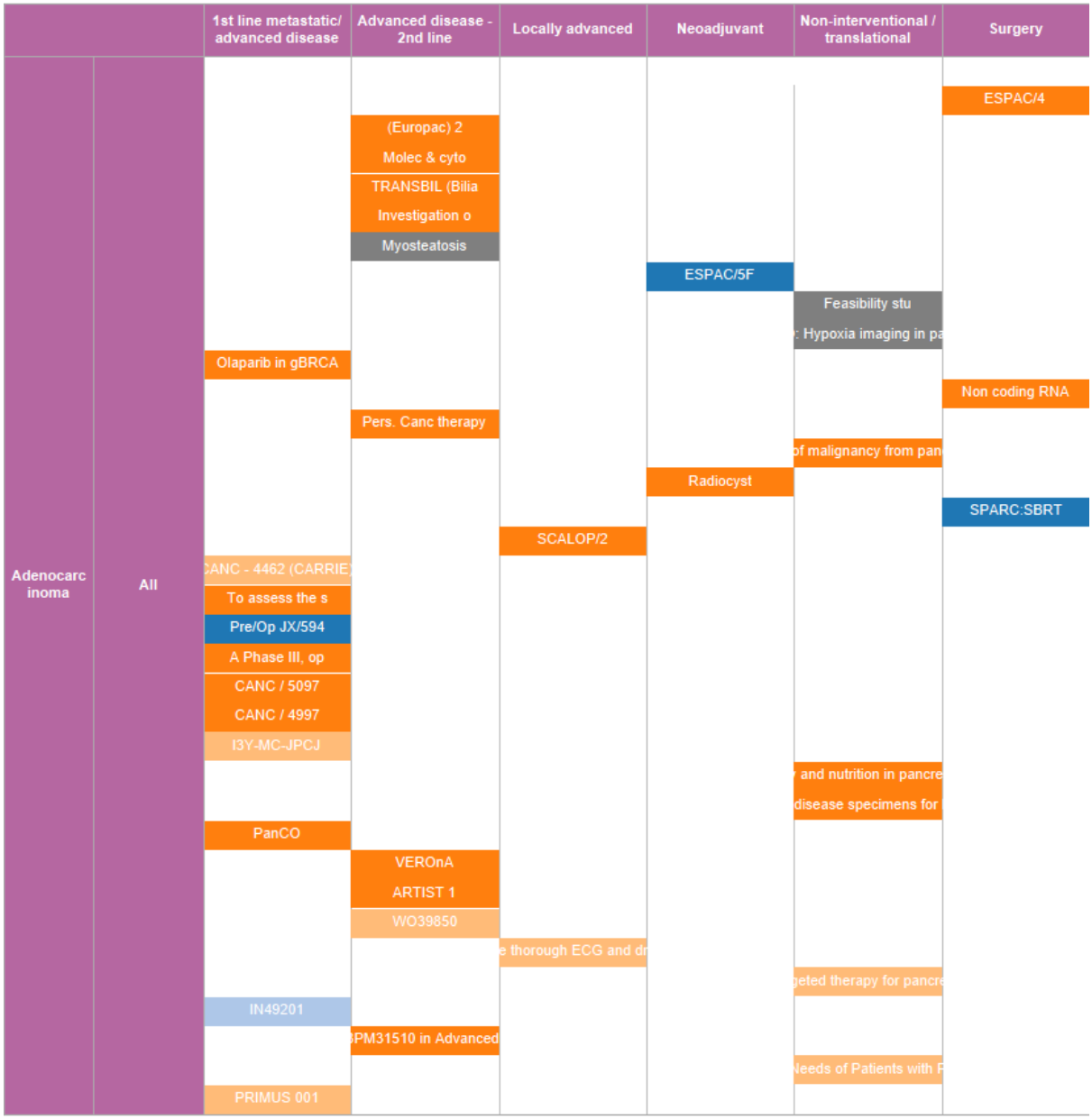
NCRI portfolio maps

Upper Gastro-Intestinal Cancer

Map E – Pancreas

Click ↓ below to reset map



Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

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Appendix 4

Top 5 publications in the reporting year

Please note that the below section is incomplete

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Neoptolemos et al, Lancet 2017 389, Page: 1011-1024		
2. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Ferolla P et al, Lancet Oncol. 2017 Dec;18(12):1652-1664	First randomised control trial to be performed in well differentiated bronchial NET. Provided new data on the combination of everolimus and pasireotide and additional data (to RADIANT 4) for the efficacy of single agent everolimus in pulmonary NET	NET Subgroup developed
3. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in	Demonstrated that the addition of pasireotide to everolimus for well differentiated PNET	Subgroup supported

advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Kulke MH et al, Ann Oncol. 2017 Jun 1;28(6):1309-1315.	improved response rates but not PFS or OS when compared to single agent everolimus.	
4. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. Cunningham D et al, Lancet Oncol. 2017 Mar;18(3):357-370		
5. Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomised trial of definitive chemoradiotherapy +/- cetuximab in oesophageal cancer. Crosby et al, British Journal of Cancer 116(6): 709-716.		

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Upper Gastrointestinal Cancer CSG portfolio, 34 trials closed to recruitment and 29 opened.

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
2013/2014	904	1866	882	1652	3.6	6.8
2014/2015	1178	1863	1092	1543	4.5	6.3
2015/2016	1303	1504	969	1236	3.98	5.07
2016/2017	1241	1806	1077	1470	4.42	6.03
2017/2018	1782	1800	1767	1741	7.25	7.14

Appendix 6

Feedback from the Quinquennial Review Panel

The Panel thanked the Upper GI CSG for the documentation provided and the openness with which they had engaged in discussions. The Panel considered at some length options for a radical restructuring of the CSG (e.g. splitting into two, for oesophagogastric and other cancers), but concluded that at this point the basic structure of the Group should remain the same.

The Panel identified a number of strengths of the Group and issues which the CSG need to consider:

Strengths

- The Panel felt that the CSG was more successful than the report indicated, had good examples of impact and should be proud of the achievements over the past five years.
- The CSG's portfolio of studies has had clear international impact and changed practice.
- The Panel congratulated the Group on the PRECISION Panc award, and felt that the oesophagogastic precision medicine bid to MRC, if successful, could be an important development.
- The Panel were pleased that, after being under-represented in the Group's past, radiotherapy research is now being recognised as an important topic.
- NETs and biliary tract were considered important areas with good work emerging from the Subgroups.

Issues for the CSG to consider

- The main CSG and Subgroups are lacking a clear Strategy, and this should be addressed with some urgency. A Strategy Day will be an important step, and should include the Group's strategic response to challenges identified through this review process.
- Screening and early diagnosis requires more focus, especially in the non-OG cancers. The Group should interact with the SPED Advisory Group and other CSGs including, but not limited to, the Primary Care CSG. The CSG should also work to collaborate with researchers in other relevant diseases, e.g. diabetology and hepatology.
- The incoming Chair will need to look at the balance of expertise on the CSG and Subgroups, and consider using the rotation/appointment system to bring in new expertise including immunotherapy, radiotherapy, radiology and gastroenterology.
- It was felt that there should be a greater link with the emerging basic research when developing trials and that this should be addressed in the new strategy and reflected in the makeup of the CSG and Subgroups.
- The Panel recommended the establishment of a vice-Chair role for the CSG which could provide additional translational research input.
- The Panel recommended learning from the successful funding of PRECISION Panc and using this model to develop work in other areas.
- The Panel agreed with the CSG that pragmatic "A-versus-B" studies addressing relevant clinical questions are still important. However, they must also capture scientific opportunities and respond to the funding environment and the current clinical research landscape, e.g. through strong translational components which might also help understand why trials are

unsuccessful and inform future research and hypothesis driven sample collections built into their design.

- Consumers were considered vital to the Group and more must be done to recruit and engage consumers, and support them to be effective and fully integrated members of the Group and Subgroups.

Issues for the NCRI/NIHR CRN to consider

- The optimum arrangements for Cancer of Unknown Primary (CUP) and Acute Oncology research to be considered at a planned NCRI Workshop.
- The NCRI CRG team will assist the Upper GI Chair and Subgroup Chairs in carrying out the recommendations of the QQR, including helping set up interactions with other groups as detailed above.
- NIHR CRN CC to work with the UGI CSG to strengthen the interactions with the Upper GI Cancer Subspecialty Leads and Divisional Research Managers at regional level (LCRNs).

In concluding the Review, Professor Seymour thanked everybody for participating and the NCRI CSG Team for preparing the paperwork and organising the Review.

The business of the meeting took four hours. ***The Group will be reviewed in five years' time.***

Set of objectives – 10 point plan

1. Hold a Strategy Day to develop a clear way forward for the CSG and Subgroups.
2. Explore opportunities for using routinely collected data.
3. Build on the existing emphasis on screening, prevention and early detection.
4. Steer the community to maximise the opportunity they have through the PRECISION Panc award.
5. Learn from the successful funding of PRECISION Panc as a model for the development of studies in other areas. Include basic sample collection with pre-planned idea for usage.
6. Embed a greater emphasis on translational research with stronger links to the emerging basic science.
7. Review the skills balance of the CSG and Subgroups to deliver on the new strategy and recommendations of this review. This includes appointments in immunotherapy, radiotherapy, radiology and gastroenterology and more effective use of consumer members (this to be supported by the NCRI Executive).
8. Consider the creation of a vice Chair role who has expertise in translational research to support this area.
9. Improve communication with the research funders to better understand their funding priorities and criteria for a successful application.
10. Use of rigorous internal peer review system within the CSG for new funding applications arising from the Subgroups.
11. Consider greater joint working with other CSGs in areas of shared interest, e.g. metastatic disease.