

## **NCRI Upper GI Clinical Studies Group**

### **Introduction**

The randomised phase III ABC02 trial completed accrual in 2008 and reported the positive finding of a statistically and clinically significant improvement in overall survival from the addition of cisplatin to gemcitabine chemotherapy for advanced biliary tract tumours at the ASCO annual meeting held in Orlando in May/June, 2009. The ABC-03 study is under development and will evaluate the addition of the small molecule tyrosine kinase inhibitor, cediranib, to chemotherapy with gemcitabine plus cisplatin.

The international randomised phase III ESPAC-3 study also completed accrual in 2008 and presented the results of the primary analysis at the ASCO annual meeting, 2009. No significant difference in overall survival was demonstrated for adjuvant gemcitabine compared to adjuvant bolus 5-FU/leucovorin for resected pancreatic cancer, although the gemcitabine was better tolerated. The ESPAC-4 study will randomise patients to adjuvant gemcitabine or gemcitabine plus capecitabine.

At the start of 2008, the results of the Upper GI CSG's REAL-2 trial were published in the New England Journal of Medicine. The study randomised 1002 patients with advanced oesophago-gastric cancer to receive one of four chemotherapy regimens, allowing comparison of capecitabine to infused 5-FU and oxaliplatin to cisplatin. The study met its primary endpoint by demonstrating non-inferiority for both the fluoropyrimidine and platinum comparisons and also demonstrated superiority of the EOX (Epirubicin, oxaliplatin and capecitabine) combination to the standard ECF regimen for overall survival in a planned secondary analysis. Based on these results and on the advice of CTAAC, EOX has replaced ECF as the standard arm of the new REAL 3 trial, which opened to recruitment in 2008.

One of the Group's major strategies has been to develop our translational research portfolio, by adding translational sub-studies to both past and future trials. This includes retrospective collection and analysis of tumour samples from trials including OE02, MAGIC and the ESPAC trials as well as prospective collection within the OE05, ST03, SCOPE, REAL3, BILCAP and New EPOC trials. The cooperation of the Principal Investigators and their pathology departments in moving these vital sub-studies forward is greatly appreciated.

The Upper GI CSG had a very successful Progress Review in June 2009. The strengths of the Group and issues for the group to address identified by the Review Panel can be found in Appendix 2.

### **Membership and structure**

No new subgroups have been created in 2008/9. Professor Cunningham's Chairmanship was extended for a further 18 months. Ms Susan Dutton and Dr Daniel Palmer joined the Group and Professor Janet Dunn stepped down from the Group during the reporting period.

### **Portfolio and accrual**

The REAL3 trial of EOX with or without panitumumab for advanced oesophago-gastric cancer opened to recruitment in May, 2008. The trial aims to recruit 730 patients from centres across the UK over 3 years and includes a translational sub-study. The COUGAR study of docetaxel versus best supportive care for the second-line treatment of advanced gastric cancer has opened to recruitment. The ST03 trial of peri-operative chemotherapy with ECX, with or without the anti-VEGF monoclonal antibody, bevacizumab for operable gastric cancer opened to

recruitment in 2007. The OE05 study of evaluating neo-adjuvant ECX chemotherapy versus standard CF chemotherapy for resectable oesophageal cancer continues to recruit well. Translational sub-studies are prospectively collecting blood and tissue samples from patients enrolled in ST03 and OE05 to identify predictive and prognostic biomarkers.

Retrospective tissue collection translational studies have opened for the OE02 and MAGIC studies. Both trials aim to identify and evaluate predictive and prognostic biomarkers.

Studies in set-up include the COG study of gefitinib versus best supportive care for the 2<sup>nd</sup>-line treatment of advanced oesophageal cancer and a feasibility study of intraperitoneal chemotherapy in localised gastric cancer with positive intraperitoneal cytology.

NET01 is a randomised phase II study comparing capecitabine plus streptozocin with or without cisplatin in the treatment of unresectable or metastatic gastroentero-pancreatic neuroendocrine tumours. The trial is expected to complete accrual of 84 patients at the end of 2009.

P4NET is an international clinical and psychometric validation of a quality of life assessment in patients with gastrointestinal neuroendocrine tumours. The study plans to recruit 400 patients; 200 within the UK. The neuroendocrine sub-group is currently considering several phase II protocols for further development.

The Prevention and Early Diagnosis Subgroup is undertaking two large RCTs; ASPECT (a chemoprevention trial, which has almost completed planned accrual of 2500 patients) and BOSS (a pilot phase (planned n=50) of this surveillance trial has opened to recruitment). Both trials will address the value of conventional endoscopic surveillance together with targeted chemoprevention. Furthermore the proposed translational studies supporting this namely CHOPIN and IPOD will assess prognostic and predictive biomarkers of response as well as inherited host genetic factors of risk.

The Chemoradiation Subgroup continues to work to develop, set up and perform CRT trials in oesophageal, gastric and pancreatic cancer: SCOPE 1, a study of cisplatin and capecitabine chemoradiation with or without cetuximab for localised oesophageal cancer unsuitable for surgery opened to recruitment in 2008. Two studies of chemoradiation following induction chemotherapy for locally advanced pancreatic cancer (SCALOP and PERU) are in set-up and will open to accrual in 2009.

The Pancreas Subgroup's TeloVac trial opened in March 2007. This is a prospective, multicentre phase III, randomised controlled trial comparing combination Gemcitabine and Capecitabine therapy with concurrent and sequential immunotherapy using the telomerase vaccine GV 1001 in patients with untreated locally advanced and metastatic pancreatic cancer. The ESPAC-4 study of gemcitabine versus gemcitabine plus capecitabine for completely resected pancreatic cancer has opened to recruitment. The ESPAC-Tplus trial has received funding from CRUK and aims to collect archived biopsy tissue and new blood samples from patients from the previous ESPAC trials as well as the current ESPAC-4 trial..

The New EPOC study plans to randomise 340 patients with resectable colorectal cancer liver metastases to peri-operative chemotherapy, with or without the anti-EGFR monoclonal antibody, cetuximab. Photostent is a randomised study evaluating the use of PDT in biliary tract cancers and has accrued over half of the planned 111 patients. The BILCAP study of adjuvant capecitabine versus observation for resected biliary tract tumours continues to accrue slowly. The Hepatobiliary Subgroup is developing a number of novel clinical trials including TACE-2, randomising patients with localised HCC to chemoembolisation, with or without the tyrosine kinase inhibitor (TKI), Sorafenib. The ABC-03 study will evaluate gemcitabine plus cisplatin

chemotherapy, with or without another TKI, cediranib. New EPOC-2 is a study planned for patients with operable liver metastases for colon cancer, whose tumours harbour a k-ras mutation, making them ineligible for the New-EPOC study.

A full list of the Group's studies can be found in Table 1 below.

**Table 1: Upper GI CSG portfolio**

Acronym	Title	PI(s)	Status
ABC 02	Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas and other biliary tract tumours: a multicentre, randomised phase III study.	Dr John Bridgewater, Dr Juan Valle, Dr Harpreet Wasan	Closed
ABC-01	Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinomas and other biliary tract tumours: a multicentre, randomised phase II study.	Dr Juan Valle	Closed
Adjuvant Stomach Chemotherapy	Post operative chemo-radiotherapy after surgical resection of gastric and oesophageal cancer. a multi-centre phase I/II study of a fixed radiotherapy regimen with concurrent chemotherapy with escalating doses of capecitabine	Dr Mark Saunders	Closed
ASPECT	ASpirin Esomeprazole Chemoprevention Trial	Professor Janusz Jankowski	Open
Barrett's Oesophagus	A sibling pair study to identify Barrett's oesophagus susceptibility genes.	Dr Rebecca Fitzgerald	Open
BILCAP	A randomised clinical trial evaluating adjuvant chemotherapy with capecitabine compared to expectant treatment alone following surgery for biliary tract cancer	Professor John Primrose	Open
BILXELOX (G185)	A phase II study of capecitabine and oxaliplatin combination chemotherapy in patients with inoperable adenocarcinoma of the gall bladder or biliary tract.	Dr Jeff Evans	Closed
BOXER	Phase II clinical trial of capecitabine and oxaliplatin plus bevacizumab as neoadjuvant treatment for patients with previously untreated unresectable liver-only metastases from colorectal cancer	Professor David Cunningham	Open

BOSS	Barratt's Oesophagus Surveillance Study	Professor Janusz Jankowski	Open
CHOPIN	Translational study Chemoprevention of intestinal premalignancy in neoplasia This study aims to assess biomarkers of tissue progression to cancer in the upper gi tract. Biopsies are collected from barrett's as well as normal gastric and oesophageal mucosa every 2 years until cancer or death. we are studying epigenetics of progression.	Professor Janusz Jankowski	Open
COG	Phase III randomised double-blind placebo-controlled trial of gefitinib 500mg once daily versus placebo in oesophageal cancer progressing after chemotherapy	Dr David Ferry	In set-up
COUGAR	A randomised phase III study of docetaxel versus active symptom control in patients with relapsed gastric adenocarcinoma	Dr Hugo Ford	Open
Development of an EORTC Quality of life module for cholangiocarcinoma	Development of an EORTC quality of life module for cholangiocarcinoma	Dr JK Ramage	Open
Enteral Nutrition Trial	A randomised controlled trial of early enteral nutrition after major gastrointestinal resection for malignancy	Ms Rachel Barlow	Open
ESPAC QLQ	Validation of the European study group for pancreatic cancer' quality of life questionnaire for patients with pancreatic cancer - the ESPAC QLQ	Professor John Neoptolemos, Mrs Jennifer Almond	Closed
ESPAC-3	Phase III adjuvant trial in pancreatic and ampullary cancer comparing 5FU/folinic acid vs. gemcitabine as adjuvant treatment	Professor John Neoptolemos	Closed
ESPAC-4	Phase III adjuvant trial randomised trial in pancreatic cancer comparing gemcitabine and capecitabine with gemcitabine alone	Professor John Neoptolemos	Open

ESPAC-T	Translational research study, using blood and biopsy tissue from patients enrolled in the ESPAC trials.	Professor John Neoptolemos	Open
FRAGEM	Phase II randomised study of chemo-anticoagulation (Gemcitabine_LMWH) vs chemotherapy alone (Gemcitabine) for locally advanced and metastatic pancreatic adenocarcinoma	Dr Anthony Maraveyas	Open
GEMCAP	A phase III multicentre randomised clinical trial comparing gemcitabine alone or in combination with capecitabine for the treatment of patients with advanced pancreatic cancer	Professor David Cunningham, Dr Janet Dunn, Professor John Neoptolemos	Closed
HEP-1	A randomised clinical trial evaluating the benefits of Doxorubicin chemoembolisation versus systemic Doxorubicin in patients with unresectable, advanced hepatocellular carcinoma.	Professor James Garden	Closed
IPOD	Inherited predisposition to oesophageal diseases. Evaluating genome wide assessment of blood samples taken on a once off visit in people with Barrett's.	Professor Janusz Jankowski	Open
MAGIC	A randomised, controlled trial of pre- and post-operative chemotherapy in patients with operable gastric cancer	Mr William Allum, Professor David Cunningham	Closed
NaTTS (Nationwide Trial of Thoracoscopic Splanchnicectomy)	An open randomised comparison of the clinical effectiveness and costs of protocol driven opioid analgesia, celiac plexus block, or thoracoscopic splanchnicectomy for pain relief in patients with abdominal malignancy	Mr Colin Johnson	Closed
NCRN012-Industry study	A phase III randomised, double-blind study of Sunitinib (SU011248, Sutent®) versus placebo in patients with progressive advanced/metastatic well differentiated pancreatic islet cell tumors		Closed
NET 01	A randomised phase II study comparing capecitabine plus streptozocin with or without cisplatin in the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours	Dr Pippa Corrie Dr Tim Meyer	Open

New-EPOC	Phase III peri-operative chemotherapy v chemotherapy plus cetuximab in patients with colorectal liver metastases (k-ras wt tumours).	Professor John Primrose	Open
NUT Study	A randomised controlled trial of nutritional intervention for patients with weight loss who are undergoing chemotherapy for gastrointestinal malignancy	Dr Jervoise Andreyev	Open
OE05	A randomised controlled trial comparing standard chemotherapy followed by resection versus ECX chemotherapy followed by resection in patients with resectable adenocarcinoma of the oesophagus	Professor David Cunningham, Professor Derek Alderson	Open
OES/STO Merge	A study to combine the EORTC quality of life questionnaire modules, the QLQ-OES18 and QLQ-STO22 to measure quality of life in patients with oesophageal or gastric cancer, or cancer of the oesophago-gastric junction	Miss Jane Blazeby	Open
P4NET	Clinical and psychometric validation of a disease specific module in assessing the quality of life of patients with G.I.-related neuroendocrine tumours.		Open
PHOTOSTENT 1	(previously BTC - PDT Phase II) Phase II trial to examine safety and efficacy of photofrin photodynamic therapy in locally advanced biliary tree carcinoma	Dr Steve Pereira	Closed
PHOTOSTENT 2	Photofrin photodynamic therapy plus stenting versus stenting alone in patients with advanced or metastatic cholangiocarcinomas and other biliary tract tumours: A multicentre, randomised, phase II/III study	Dr Steve Pereira	Open
Quality of Life in secondary liver	(a) Development of an EORTC QoL questionnaire for patients with malignant carcinoid tumours. (b) A study of the clinical and psychometric validation study of a disease-specific questionnaire module(QLQ-LMC21) in assessing the quality of life of patients with liver metastases from colorectal cancer	Mr Rees, Dr JK Ramage	Open
REAL 2	A phase II/III randomised trial comparing Epirubicin, Cisplatin & Protracted Venous Infusion (PVI) 5-	Professor David Cunningham	Closed

	Fluorouracil (ECF) with Epirubicin, Oxaliplatin & PVI 5-FU (EEF), Epirubicin, Cisplatin and Capecitabine (ECX) with Epirubicin, Oxaliplatin & Capecitabine		
REAL3	A randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer	Professor David Cunningham	Open
RECaD	Raman spectroscopy for cancer and pre-cancer detection in the oesophagus	Dr Nicholas Stone	Open
SCALOP	Randomised phase 2 study of gemcitabine or capecitabine in combination with RT for selected patients with locally advanced inoperable pancreatic tumour (LANPC).	Dr S Mukherjee	Set-up
SCOPE1	Study of Chemoradiotherapy in Oesophageal Cancer Plus or Minus Erbitux	Dr Tom Crosby	Open
SOCS	Stomach and Oesophageal Cancer Study	Professor Carlos Caldas,	Open
ST-03	A randomised phase III study of peri-operative chemotherapy with or without bevacizumab in patients with operable adenocarcinoma of the stomach and gastro-oesophageal junction	Professor David Cunningham, Professor Derek Alderson	Open
STENTS	A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with oesophageal cancer	Professor M Griffin	Closed
TACE	A phase II/III randomised controlled trial of trans-arterial chemoembolisation versus embolisation alone in non-resectable hepatocellular carcinoma.	Dr Tim Meyer	Open
TARGET Trial	Phase I-II dose finding and early efficacy study of combination therapy with Erlotinib (Tarceva), Gemcitabine, Bevacizumab (Avastin), and Capecitabine in advanced pancreatic cancer.	Professor David Cunningham	Closed

TeloVac	A prospective, phase III, controlled, multicentre, randomised clinical trial comparing combination gemcitabine and capecitabine therapy with concurrent and sequential chemoimmunotherapy using a telomerase vaccine in locally advanced and metastatic pancreatic cancer	Dr Gary Middleton	Open
Thalidomide in cancer cachexia	The use of thalidomide as a treatment for cancer cachexia	Dr Susi Green	Open
Trans-MAGIC	Tumour expression of prognostic and predictive factors in a randomised trial of peri-operative chemotherapy for gastric cancer	Dr Andy Wotherspoon	Open
Trans-OE02	Prognostic and predictive factors in a randomised controlled clinical trial of pre-operative chemotherapy in respectable oesophageal patients	Dr Heike Grabsch	Open
Upper GI Quality of Life Study	Quality of life and satisfaction with care in patients with cancers of the oesophagus, stomach and pancreas	Miss Jane Blazeby	Open

2865 patients were recruited to Upper GI studies in 2008/09, representing 12.3% of total of incident cases. 1712 were to RCTs, 7.3% of disease incidence and 1153 were to non-RCTs, 4.9% of disease incidence.

### **Trials in development**

The Group has a number of trials in development/set up:

- SCALOP (Selective Chemoradiation in Advanced Localised Pancreatic cancer) is a randomised phase 2 study of gemcitabine or capecitabine in combination with RT for selected patients with locally advanced inoperable pancreatic tumour (LANPC). Patients with histologically proven LAPC and fit to receive CRT with stable or localised disease after 4 months of Gemcitabine/Capecitabine Chemotherapy will be randomised to either gemcitabine or capecitabine-based chemoradiation. The Chief Investigator (CI) is Dr S Mukherjee, Velindre Hospital, and the co-ordinating centre Wales Cancer Trials Unit.
- The PERU trial is a multicentre randomised phase II clinical study of UFT/leucovorin, radiotherapy with or without cetuximab following induction gemcitabine plus capecitabine in patients with locally advanced pancreatic cancer (Pancreatic cancer Erbitux, Radiotherapy and UFT). The study's CI is Dr Ian Chau and the sponsor, The Royal Marsden NHS Foundation Trust. The planned recruitment is to randomise 90 patients (45 in each arm) and planned start date July 2009. The recruitment period is 18 months and patients will be followed up in clinic for 5 years after completion of treatment
- CYT-6091 is a phase I/II two-part dose finding and early efficacy study of cyt-6091 in combination with gemcitabine in patients with pancreatic cancer. The target Accrual is 40 and the estimated recruitment period, 24 months
- ESPAC 4Tplus is a translational study to collect and store samples from ESPAC-4 trial. A TRICC application will be submitted in July 2009.

- Barrett's Esophagus Ablation Trial (BEAT) is a randomised study in 350 patients of endoscopy / endotherapy alone versus surgery alone. The CI is Dr John deCaestecker from Leicester.
- Aspirin Chemoprevention for Everyone (ACE) is a 50,000 patient primary prevention trial RCT to standard acid suppression alone or acid suppression and low dose aspirin. The CI is Professor Janusz Jankowski and Dr Brendan Delaney.
- The TACE 2 trial of chemoembolisation with or without Sorafenib for patients with inoperable, non-metastatic hepatocellular carcinoma will be run from the Birmingham CTU when it opens in 2009. Opening of this study is imminent. The Chief Investigator is Dr Tim Meyer.
- ABC-O3 is a 120-patient randomised phase II study to assess the activity of the CisGem regimen from ABC-02 with Cedirinib, a small molecule VEGF inhibitor. If activity is suggested, it is planned that the trial be converted into a randomised phase III design. This study is currently in development, the Chief Investigator is Dr Juan Valle.
- New EPOC-2. is a planned randomised phase II study in patients suitable for the EPOC trial but have tumours with a k-ras mutation. The proposal is to compare perioperative chemotherapy with post operative chemotherapy in patients with operable colorectal liver metastases. This study is currently in development. The Chief Investigator is Professor JN Primrose.
- The Neuroendocrine Subgroup is considering a number of potential phase II studies including Capecitabine / Temozolomide vs. leading arm of NET01 study Or Sunitinib vs. leading arm of NET01 study, Yttrium-90 SIR spheres vs. particle embolisation alone for treatment of liver metastases in NETs, Yttrium-90 DOTA Octreotate + capecitabine vs Yttrium-90 DOTA Octreotate alone in patients with metastatic midgut NET and ZA , a new small molecule vs. Sandostatin LAR in patients with midgut carcinoid

### Meetings

The Upper GI CSG held its Annual Trials Meeting in October 2008. This was well attended and received positive feedback. The next Upper GI Annual Trials Meeting is scheduled to be held on 15<sup>th</sup> of October 2009.

### Collaborations

The Upper GI CSG has had a long-standing successful collaboration with the ESPAC group, which will continue with the opening of the ESPAC-4 trial. There is international collaboration planned with centres in Australia for the ABC-03 trial.

Within the NCRI, the Upper GI CSG has conducted trials with the Colorectal CSG, Radiotherapy CSG and the newly created NCRI Clinical and Translational Radiotherapy Research Working Group (CTRRWG). For example, the New EPOC study in patients with liver metastasis from colorectal cancer is collaboration with the Colorectal CSG. The Upper GI Prevention and Early Diagnosis Subgroup is also collaborating with Colorectal Prevention and Screening Subgroup on the ACE trial.

### 3-year strategy

The 3-year strategy remains:

- **Portfolio development:** The major strategy over the past five years has been to develop a robust clinical trial portfolio addressing the areas of greatest clinical need. This has included establishing clinical trials in relatively uncommon tumours such as cholangiocarcinoma, neuroendocrine tumours and hepatocellular carcinoma. The Group

remains committed to maintaining and developing the clinical trials portfolio and ensuring that we continue to meet the needs of these rarer tumour types as well as those which are more prevalent.

- **Collaboration:** We have forged successful relationships with the pharmaceutical industry, bringing new funding to the NCRN through clinical trials such as ST03 and REAL3. These links are vital to gaining access to targeted agents and ensuring that our trials are at the forefront of international research in Upper GI cancers.
- **Translational research:** Our main priority is to consolidate and further develop the links in molecular pathology leading to an improved ability to conduct high quality translational studies. The retrospective and prospective collection of tumour samples from our large phase III trials will provide vital information to inform future trial design and potentially reshape our clinical practice, allowing us to personalise cancer care in the future. The cooperation of the NCRN is key to ensuring the success of these projects.

Professor David Cunningham, Chair

## Appendix 1

### 2008/09 Publications and abstracts

#### **Chemoradiation Subgroup**

**T Crosby, M Evans.** Management of a patient with an operable T3N1 carcinoma oesophagus-  
*an oncologists view. In Press 2009*

**T Crosby, M Evans.** The Management of Locally Advanced Carcinoma of the Oesophagus-  
SCOPE for improvement? *Clin Onc 2009 EPUB*

**M Evans, T Crosby.** Oesophageal cancer: current trends and management. *J R Coll Physicians  
Edinb 2008; 38:242–5*

**Morgan MA, Twine C, Lewis WG, Lambe R, Oliphant HE, Barry JD, Robinson M, Crosby T,  
Roberts SA.** Prognostic significance of failure to cross esophageal tumours by endoluminal  
ultrasound. *Dis Esophagus 2008 Sep; 21(6):508-513.*

**Morgan MA, Lewis WG, Casbard A, Roberts SA, Adams R, Clark G, Havard T, Crosby T.**  
Prospective cohort stage for stage comparison of definitive chemoradiation, surgery alone and  
neoadjuvant chemotherapy for oesophageal carcinoma. *Br J Surg 2009 (in press).*

**Twine CP, Barry J, Blackshaw G, Roberts SA, Crosby T, Lewis WG.** Prognostic significance  
of EUS defined fluid effusions in patients with oesophageal cancer. *Surg Endoscopy 2009 (in  
press).*

**Twine CP, Roberts SA, Chan D, Crosby T, Robinson M, Lewis WG.** Prognostic significance  
of endoluminal ultrasound (EUS) defined tumour volume in patients diagnosed with oesophageal  
cancer. *Ann Surg 2009.*

**Twine CP, Lewis WG, Morgan MA, Chan D, Clark GWB, Havard TJ, Crosby T, Roberts SA,  
Williams GT.** The prognosis of surgically resected oesophageal cancer is dependent on the  
number of lymph nodes examined. *J Path 2008.4*

#### **Pancreas Subgroup**

**Campbell F, Smith RA, Whelan P, R Sutton, Raraty M, Neoptolemos JP, Ghaneh P.**  
Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour  
involvement within 1 mm of a resection margin. *Accepted Histopathology February 2009*

**R Carter, DD Stocken P Ghaneh, S Bramhall, A Olah, D Kelemen, C Bassi, H Friess, C  
Dervenis, L, MW Büchler, JP Neoptolemos.** Longitudinal Quality of Life Data can provide  
Insights on the Impact of Adjuvant Treatment for Pancreatic Cancer – Subset Analysis of the  
ESPAC-1 Data. *Int J Cancer. 2009;124(12):2960-2965.*

**Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M,  
Padbury R, Doi R, Smith D, Büchler MW.** Adjuvant 5-fluorouracil and folinic acid versus  
observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) Trials. *Br J  
Cancer 2009;100:246-50.*

**Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P.** Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg.* 2009 Apr;197(4):466-72.

**Naureen Starling, David Watkins, David Cunningham, Janet Thomas, Janine Webb, Gina Brown, Karen Thomas, Jacqui Oates and Ian Chau** Dose Finding and Early Efficacy Study of a Chemotherapy Doublet (Gemcitabine plus Capecitabine) in Combination with a Biologic Doublet (Bevacizumab plus Erlotinib) in Advanced Pancreatic Cancer. *Journal of Clinical Oncology* 2009 (in press)

**Sultana A, Shore S, Vinjamuri S, Evans JC, Tudur Smith C, Chauhan S, Bosonnet L, Garvey C, Neoptolemos JP, Ghaneh P.** Randomised Phase I/II trial assessing the safety and efficacy of radio labelled anti-carcinoembryonic antigen antibodies given intra-arterially or intravenously in patients with unresectable pancreatic adenocarcinoma. *BMC Cancer.* 2009; 9: 66.

**Halloran C, Ghaneh P, Connor S, Bossonet L, Sutton, R, Neoptolemos JP, Raraty MGT.** Carbohydrate antigen 19.9 accurately selects patients for laparoscopic assessment to determine resectability of pancreatic malignancy. *Br J Surg.* 2008;95:453-9

**Smith RA, Ghaneh P, Sutton R, Raraty M, Campbell F, Neoptolemos JP.** Prognosis of Resected Ampullary Adenocarcinoma by Preoperative Serum CA19-9 Levels and Platelet-Lymphocyte Ratio. *J. Gastrointest Surg.* 2008 ;12(8):1422-8.

**Smith RA, Bosonnet L, Ghaneh P, Sutton R, Evans J, Healey P, Garvey C, Hughes M, Raraty M, Campbell F, Neoptolemos JP** The platelet-lymphocyte ratio improves the predictive value of serum CA19-9 levels in determining patient selection for staging laparoscopy in suspected periampullary cancer. *Surgery.* 2008;143:658-66.

**Smith RA, Bosonnet L, Ghaneh P, Raraty M, Sutton S, Campbell F, Neoptolemos JP...** Preoperative CA19-9 Levels and Lymph-Node Ratio are Independent Predictors of Survival in Patients with Resected Pancreatic Ductal Adenocarcinoma. *Dig Surg.* 2008 Jun 24;25(3):226-232

**Smith RA, Dajani K, Dodd S, Whelan P, Raraty M, Sutton R, Campbell F, Neoptolemos JP, Ghaneh P.** Pre-operative resolution of jaundice following biliary stenting predicts more favourable early survival in resected pancreatic ductal adenocarcinoma. *Ann Surg Oncol.* 2008;15:3138-46.

**Starling N, Cunningham D.** Survival from cancer of the pancreas in England and Wales up to 2001. *Br J Cancer.* 2008 Sep 23;99 Suppl 1:S24-5.

**Sultana A, Neoptolemos JP, Frauscher F, Ghaneh P.** Gemcitabine-Based Combination Chemotherapy in the Treatment of Advanced Pancreatic Cancer. *Am J Hematology/Oncology* 2008; 7: 96-100.

**Sultana A, Tudur Smith C, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P..** Meta-Analyses of Chemotherapy for Locally Advanced and Metastatic Pancreatic Cancer- Results of secondary endpoints analyses. *Br J Cancer.* 2008 Jul 8;99(1):6-13

**Sultana A, Ghaneh P, Cunningham D, Starling N, Neoptolemos JP, Tudur Smith C.** Gemcitabine based combination chemotherapy in advanced pancreatic cancer- Indirect comparison. *BMC Cancer* 2008, 8:192.

#### **Hepatobiliary Subgroup**

**JW Valle, HS Wasan, DD palmer, D Cunningham, DA Anthoney, A Maraveyas, SK Hughes, M Roughton, JA Bridgewater.** Gemcitabine with or without cisplatin in patients with advanced or metastatic biliary tract cancer (ABC): Results of a multicentre, randomised phase III trial (the UK ABC-02 trial). *ASCO Annual Meeting 2009, abstract 4503.*

**Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T;** EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet.* 2008 Mar 22;371(9617):1007-16.

#### **Oesophagogastric Subgroup**

**Ian Chau, Sue Ashley and David Cunningham.** Validation of the Royal Marsden Hospital Prognostic Index in Advanced Esophagogastric Cancer Using Individual Patient Data from the REAL 2 Study. Ian Chau, Sue Ashley and David Cunningham. *Journal of Clinical Oncology* (2009: Epub ahead of print)

**I Chau, AR Norman, Cunningham et al.** The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma—individual patient data from 1775 patients in four randomised controlled trials. *Annals of Oncology* (2009) 20: 885–891, 2009

#### **AFC Okines, AR Norman, P McCloud, Y-K. Kang and D. Cunningham**

Meta-analysis of the REAL-2 and ML17032 Trials: Evaluating Capecitabine-based Combination Chemotherapy and Infused 5-Fluorouracil-based Combination Chemotherapy for the Treatment of Advanced Oesophago-gastric Cancer. *Annals of Oncology* (2009: In press)

**Starling N, Okines A, Cunningham D, Allum W, Wotherspoon A, Benson M, Thompson J, Thomas J, Brown G, Riddell A, Stavridi F, Ashley S, Oates J, Chau I** A phase II trial of preoperative chemotherapy with epirubicin, cisplatin and capecitabine for patients with localised gastro-oesophageal junctional adenocarcinoma. Starling N, Okines A, Cunningham D et al., *British Journal of Cancer.* (2009) May 12. (Epub ahead of print)

**Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR.** Thromboembolism in Patients With Advanced Gastroesophageal Cancer Treated With Anthracycline, Platinum, and Fluoropyrimidine Combination Chemotherapy: A Report From the National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. *J Clin Oncol.* 2009 Apr 27

**Wong R, Cunningham D.** Optimising treatment regimens for the management of advanced gastric cancer. *Ann Oncol.* 2009 Apr;20(4):605-8.

**Barbour AP, Lagergren P, Hughes R, Alderson D, Barham CP, Blazeby JM.** Health-related quality of life among patients with adenocarcinoma of the gastro-oesophageal junction treated by gastrectomy or oesophagectomy. *Br J Surg* 2008 Jan;95(1):80-4.

**Chau I, Norman AR, Cunningham D, Oates J, Hawkins R, Iveson T, Nicolson M, Harper P, Seymour M, Hickish T.** The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma--individual patient data from 1775 patients in four randomised controlled trials. *Ann Oncol.* 2009 May;20(5):885-91.

**Cunningham D, Starling N, Rao S et al.** Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008 Jan 3;358(1):36-46

**Cunningham D, Oliveira J** Gastric cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up.; ESMO Guidelines Working Group. *Ann Oncol.* 2008 May;19 Suppl 2:ii23-4.

**Leary A, Assersohn L, Cunningham D, Norman AR, Chong G, Brown G, Ross PJ, Costello C, Higgins L, Oates J.** A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. *Cancer Chemother Pharmacol.* 2008 Dec 23.

**Okines A, Chau I, Cunningham D.** Capecitabine in gastric cancer. *Drugs Today (Barc).* 2008 Aug;44(8):629-40. Review.

**Okines A & Cunningham D,** Progress in the multidisciplinary treatment of gastrointestinal cancers, impact on clinical practice: peri-operative management of gastro-oesophageal cancer. *Ann Oncol.* 2008 Sep;19 Suppl 7:vii259-65.

**Okines A, Chau I, Cunningham D.** Capecitabine in gastric cancer. *Drugs Today (Barc).* 2008 Aug;44(8):629-40. Review.

**Okines A & Cunningham D.** Progress in the multidisciplinary treatment of gastrointestinal cancers, impact on clinical practice: peri-operative management of gastro-oesophageal cancer. *Ann Oncol.* 2008 Sep;19 Suppl 7:vii259-65

**Rao S, Cunningham D.** Survival from cancer of the stomach in England and Wales up to 2001. *Br J Cancer.* 2008 Sep 23;99 Suppl 1:S19-20.

**Rao S, Starling N, Cunningham D, Benson M, Wotherspoon A, Lüpfer C, Kurek R, Oates J, Baselga J, Hill A.** Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. *Br J Cancer.* 2008 Sep 16;99(6):868-74

**Rao S, Starling N, Cunningham D, Benson M, Wotherspoon A, Lüpfer C, Kurek R, Oates J, Baselga J, Hill A.** Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. *Br J Cancer.* 2008 Sep 16;99(6):868-74

**Ratnayake G, Cunningham D.** Does combining docetaxel with cisplatin and fluorouracil improve clinical benefit in advanced gastroesophageal cancer? *Nat Clin Pract Oncol.* 2008 Mar;5(3):132-3

**Prevention and Early Diagnosis Subgroup**

**Jack Cuzick, Florian Otto, John A Baron, Powel H Brown, John Burn, Peter Greenwald, Janusz Jankowski, Carlo La Vecchia, Frank Meyskens, Hans Jörg Senn, Michael Thun.** Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol* 2009 (in press).

**Das D, Jankowski J.** Prevention of Colorectal Cancer by Combining Early Detection and Chemoprevention. *Current Colorectal Cancer Reports* 2009;5:48–54

**Susi Green, Ashref Tawil, Hugh Barr, Cathy Bennett, Pradeep Bhandari, John DeCaestecker, Krish Ragunath, Rajvinder Singh, Janusz Jankowski.** Radical surgery versus endotherapy for early cancer or high grade dysplasia in Barrett's oesophagus. *Cochrane Collaboration* 2009 Apr 15;(2):CD007334.

**Jankowski JA Talley NJ.** Dissecting phenotype genotype relationships in GI disease; a SNP here and a SNP there (review). *Am J Gastroenterology* 2009;104:286-8

**Jankowski J, Odze R.** Biomarkers in gastroenterology; between hype and hope comes histopathology (review). *Am J Gastroenterol* 2009;104:1094-97

**Leedham SJ, Graham TA, Oukrif D, McDonald SA, Rodriguez-Justo M, Harrison RF, Shepherd NA, Novelli MR, Jankowski JA, Wright NA.** Clonality, founder mutations and field cancerization in ulcerative colitis-associated neoplasia. *Gastroenterology* 2009 136:542-50.

**Attwood S, Preston S, Harrison LA, Jankowski J.** Esophageal adenocarcinoma in mice and men; back to basics! (review). *Am J Gastroenterol* 2008;103:2367-2372.

**Das D, Ishaq S, Harrison R, Kosuri K, Harper E, deCaestecker J, Sampliner R, Attwood S, Barr H, Watson P, Moayyedi P, Jankowski J.** Management of Barrett's oesophagus in the UK: over treated, and under biopsied but improved by a national randomised trial. *Am J Gastroenterol* 2008;103:1079-89.

**Falk GW, Jankowski J.** Chemoprevention and Barrett's Esophagus: decisions, decisions. *Am J Gastroenterology* 2008;103:1-3.

**Jankowski J.** Round table discussion: nutrition and cancer prevention for clinical trials. *Int J Probiot Prebiot* 2008;3:169-170.

**Jankowski J, Hunt R.** Cyclooxygenase-2 inhibitors in colorectal cancer prevention; better the devil you know. (review) *Cancer Epidemiology Biomarkers & Prevention* 2008;17:1858-61.

**Leedham SJ, Preston SL, McDonald SAC, Elia G, Bhandari P, Poller D, Harrison R, Novelli MR, Jankowski JA, Wright NA.** Individual crypt genetic heterogeneity and the origin of metaplastic glandular epithelium in human Barrett's esophagus. *Gut* 2008;57:1041-1048.

**McDonald S, Greaves LC, Gutierrez-Gonzalaz L, Rodriguez-Justo M, Deheragoda M, Leedham SJ, Taylor RW, Lee CY, Preston SL, Lovell M, Hunt T, Elia G, Oukrit D,**

**Harrison R, Novelli M, Mitchell I, Stoker DL, Turnbull D, Jankowski JA, Wright N.** Mechanisms of field cancerization in the human stomach: the expansion and spread of mutated gastric stem cells. *Gastroenterology* 2008;134:500-510.

**Milicic A, Harrison LA, Goodlad RA, Hardy RG, Nicholson AM, Presz M, Sieber O, Santander S, Pringle JH, Mandir N, East P, Obszynska J, Sanders S, Piazeulo E, Shaw J, Harrison R, Tomlinson IP, McDonald SAC, Wright NA, Jankowski JAZ.** Ectopic expression of P-Cadherin correlates with promoter hypomethylation early in colon carcinogenesis and enhanced intestinal crypt fission in vivo. *Cancer Research* 2008;68:7760-8.

**Moayyedi P, Burch N, Akhtar-Danesh N, Enaganti SK, Harrison R, Talley NJ, Jankowski JA.** Mortality rates in patients with Barrett's oesophagus. *Aliment Pharmacol Ther* 2008;27:316-20.

**Robertson EV, Jankowski JA.** Genetics of Gastroesophageal Cancer: paradigms, paradoxes and prognostic utility (review). *Am J Gastroenterol* 2008;103:443-9.

## Appendix 2

### Key strengths and issues from the Progress Review June 2009

The Upper GI CSG had its first 3 year review in November 2005 and its second review on 16<sup>th</sup> June 2009.

The key strengths of the Group identified at the June review were:

- *Attendance of all subgroup chairs at the review*
- *Being a very successful group of high international standing*
- *Having a track record of successfully completing clinical practice changing research, presenting and publishing it*
- *The outcomes from research having a major impact both nationally and internationally on clinical practice*
- *A broad portfolio which is up to date and which has expanded since the last review to include translational research, screening and prevention and neuroendocrine studies*
- *Working well as a group*
- *Having a clear subgroup structure which is well understood, functioning and productive*
- *Strong leadership at both main and subgroup level*
- *Clarity of future direction and having anticipated the personalised approach to medicine and the need to develop studies which will facilitate the establishment of this practice*
- *A good track record of grant submissions*
- *A significant publication record*

The Chair was commended for the way he has enabled the Group to progress, as this is no mean task given the complex area of work in which there are some “big players” with strong independent minds.

The Panel identified the following issues which the Upper GI CSG needs to consider:

- *Potential opportunities to use the greater number of radiotherapy sensitisers in tumour sites other than oesophageal e.g. pancreas*
- *Whether chemoradiation trials should be developed and be included in each of the Group’s site specific subgroups*
- *How best to engage with the PET initiative*
- *Which tissue collections would take priority if funding becomes a limiting factor*
- *Keeping in view the need to positively encourage young researchers and finding opportunities for them to be involved in the Group’s activities*
- *Identifying opportunities to explicitly demonstrate the Group’s commitment to inclusivity and the development of the next generation of trialists*
- *Setting in place a clear strategy for succession planning for both the Chair and Subgroup chairs*

The Panel agreed that the NCRN/I need to:

- *Be aware of the difficulties surrounding the use of PET in trials and to take steps to help the Group*