

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

In the past year, the positive results of two large randomized trials conducted by the Upper GI Clinical Studies Group (CSG), the REAL2 (in advanced oesophago-gastric cancer) and GEMCAP (in advanced pancreatic cancer), were presented as oral presentations at the American Society of Clinical Oncology (ASCO) 2006 Annual Meeting (Atlanta, Georgia) and the 13<sup>th</sup> European Cancer Conference (Paris) respectively. The results of the MAGIC trial (perioperative chemotherapy in resectable gastric and lower oesophageal adenocarcinoma) have also been accepted for publication in the New England Journal of Medicine. These trials have shown the ability of the CSG to conduct trials which will influence clinical and trials practice in their respective disease settings on an international level. The Group held a successful Annual Trials Meeting in July 2005.

The REAL2 study randomized a thousand patients with oesophago-gastric cancer amongst four treatment arms based on the substitution of oral capecitabine for 5-fluorouracil (5FU), and oxaliplatin for cisplatin, in the ECF regimen (epirubicin, cisplatin and protracted venous infusion 5-fluorouracil) in a 2x2 comparison. The study's planned primary end point of demonstrating non-inferiority for the fluoropyrimidine and platinum substitutions was met, particularly supporting the use of capecitabine in place of PVI 5FU in these regimens. This should improve the convenience, acceptability and safety of treatment because routine use of in dwelling intravenous access and an infusion pump is no longer required for treatment administration. In addition, a planned comparison of each individual arm suggests that the EOX arm (epirubicin, oxaliplatin and capecitabine) is the most efficacious.

In advanced pancreatic cancer, GEMCAP was one of two randomized trials reported recently which was able to show that gemcitabine based combination treatment improves survival in this disease. This is a significant achievement, as a plethora of trials of combination treatment have previously failed to improve on the survival results from treatment with single agent gemcitabine alone. These results suggest that the gemcitabine-capecitabine regimen used in this study should be one of the standard treatment options for these patients, particularly in the United Kingdom.

### **Membership**

In the past year, the Clinical Studies Group has welcomed several new members: Dr Heike Brabsch (Histopathologist), Mr Robert Hutchins (Surgeon), Dr Juan Valle (Medical Oncologist) and Dr Edward Leen (Consultant Radiologist). The group is also grateful to Dr Adrian Crellin (Clinical Oncologist) and Dr Marianne Nicolson (Medical Oncologist), who have left the group. The Chair was re-appointed for a further 3 years in June 2006.

### **Progress Review**

The Group had a Progress Review on the 9<sup>th</sup> November 2005. The key strengths of the Group and issues which the Group need to address as identified by the Review Panel are attached as an appendix.

### **Portfolio and accrual**

Several planned trials in the CSG's portfolio have now opened for recruitment. This includes the ABC02 and BILCAP studies in cancers of the biliary tract, the NET01 study in advanced gastroenteropancreatic neuroendocrine tumours and the HEP-1 trial in

unresectable hepatocellular carcinoma. Other ongoing randomized trials include the OE05 study of pre-operative treatment in resectable oesophageal cancer and the nutritional intervention NUT study. Following publication of the ESPAC1 trial in which the observed 2-year survival rate with adjuvant chemotherapy in resected pancreatic cancer was higher than initially predicted, the recruitment of the ESPAC3(v2) study of adjuvant chemotherapy was extended in February 2006 on the recommendation of the Independent Data and Safety Monitoring Committee in order to meet the agreed power of 90%. ESPAC3(v2) is now anticipated to complete accrual in the final quarter of 2006. Accrual was 3.7% of incident cases.

The TeloVac randomized trial is expected to open to accrual in the near future, as is the follow-up study to MAGIC, the MAGIC-B (ST03) and SCOPE1. TeloVac will evaluate the addition of chemoimmunotherapy with a telomerase vaccine in addition to gemcitabine and capecitabine as treatment for patients with advanced pancreatic cancer, whereas MAGIC-B will randomize patients with resectable gastric cancer to peri-operative treatment with or without the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab. SCOPE1 will randomize patients with oesophageal cancer to chemoradiotherapy with or without the anti-epidermal growth factor receptor antibody cetuximab. Studies which are being developed for the trials portfolio include the REAL3 study in advanced oesophago-gastric cancer, and the follow up studies to ESPAC3.

### **Strategy**

The following are areas which the Upper GI CSG intends to develop in the immediate future:

- *To engage the wider oncology community to generate awareness of clinical trials, of the need for clinical research and the importance of including patients in clinical trials:* This is an ongoing concern which is of importance because of the great need for progress in the treatment of upper GI cancers. In addition to continuing to develop a balanced trials portfolio, the group needs to generate enthusiasm for trials participation through its meetings and by ensuring representation within the group from the various specialists who treat upper GI cancers and representation from every corner of the United Kingdom.
- *Systematic evaluation of targeted agents:* The forefront of clinical trials in oncology is shifting away from primarily cytotoxic chemotherapy based treatments to treatment combinations or strategies which include the novel targeted agents, such as the monoclonal antibodies and tyrosine kinase inhibitors. This is particularly relevant in the upper GI cancers in which further significant progress with cytotoxic chemotherapy alone seems increasingly unlikely. The groups trials portfolio already includes several trials such as MAGIC-B/ST-03, TeloVac and TARGET which incorporate novel therapeutics. Over the next 3 years, other planned studies will see the inclusion of targeted agents into other randomized trials, such as the REAL3 trial which is currently being planned.
- *To identify subsets of patients more likely to benefit from treatment or more likely to suffer toxicity from targeted agents:* With the increasing understanding of the potential factors at a molecular or genetic level which drive the progression of cancers, new treatment targets are being identified, as are markers which may help determine patients' prognoses or likelihood of benefit from particular treatments. Other markers may also predict the susceptibility of patients to treatment related toxicities. Research in these areas will help develop tools which

clinicians may eventually use to tailor treatment to individual patients. Translational substudies are already being developed from some of the recently completed large randomized trials which the group has conducted or is conducting, such as the MAGIC, OE05 and ESPAC trials. Over the next 3 years, the group aims to include similar research as components of new trials being added to the trials portfolio.

- *Develop research protocols for relatively rare tumour types:* Several studies aimed at the rare upper GI tumour types such as biliary tract cancers (ABC-02 and BILCAP), ampullary carcinomas (ESPAC3) and neuroendocrine tumours (NET-01) have recently opened to recruitment. The group will continue to ensure that the research needs to tumour types such as these will continue to be met as an ongoing concern.
- *Develop links with other international research groups to facilitate collaborative recruitment to clinical trials requiring large patient numbers or in relatively rare disease types:* The need for adequately powered randomized trials has been emphasized by the recent reporting of trials such as MAGIC, GEMCAP and REAL2. As many upper GI trials have traditionally been relatively difficult to recruit to, the need for collaboration outside the UK is increasingly clear. Already the ESPAC trials have been conducted as part of a wider European trials group. Over the next 3 years, the group intends to develop further international collaborations for suitable studies, particularly with other research groups in Europe and Australasia. For example, the MAGIC-B/ST-03 study has attracted wide international interest in study participation and is anticipated to involve countries such as the Netherlands, Spain, France, Australia and New Zealand.

### Upper GI Group 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	Open
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	Open
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	Professor John	Open

	adjuvant chemotherapy with capecitabine compared to expectant treatment alone following surgery for biliary tract cancer	Primrose	
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
COGNATE	Cancer of the oesophagus or gastricus: new assessment of the technology of endosonography.	Professor Ian Russell	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 Cancer Comparing 5FU and D-L-Folinic Acid vs. Gemcitabine vs. No Adjuvant Treatment	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	Open
MAGIC	A randomised, controlled trial of pre- and	Mr William	Closed

	post-operative chemotherapy in patients with operable gastric cancer	Allum, Professor David Cunningham	
MAGIC-B/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	In set-up
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	Open
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
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
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	In set-up
Quality of Life in secondary liver	(a) Development of an EORTC QoL questionnaire for patients with malignant	Mr Rees, Dr JK Ramage	Open

tumours	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		
REAL 2	A phase II/III randomised trial comparing Epirubicin, Cisplatin & Protracted Venous Infusion (PVI) 5-Fluorouracil (ECF) with Epirubicin, Oxaliplatin & PVI 5-FU (EEF), Epirubicin, Cisplatin and Capecitabine (ECX) with Epirubicin, Oxaliplatin & Capecitabine	Professor David Cunningham	Closed
RECaD	Raman spectroscopy for cancer and pre-cancer detection in the oesophagus	Dr Nicholas Stone	Open
SCOPE1	Study of Chemoradiotherapy in Oesophageal Cancer Plus or Minus Erbitux	Dr Tom Crosby	In set up
SOCS	Stomach and Oesophageal Cancer Study	Prof Carlos Caldas,	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	Open
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	In set up
Thalidomide in cancer cachexia	The use of thalidomide as a treatment for cancer cachexia	Dr Susi Green	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

Professor David Cunningham, Chair

## **Appendix 1: Key strengths and issues from the Progress Review, October 2005**

### Strengths:

- The Upper GI CSG is a very successful group, which is functioning well and respected internationally.
- The Chair is a strong, exceptional and charismatic leader who has successfully coordinated a group, which contains a number of strong personalities.
- Excellent subgroup chairs that are acknowledged as international experts in their own right.
- The Group is inclusive and encourages input from young enthusiastic researchers and is successful in keeping the Upper GI community on board.
- Subgroup structure is clearly understood and it is very effective in generating new trial ideas and protocols.
- Appropriate and broad portfolio of studies producing very interesting results and set new international standards for clinical practice.
- Good publication record resulting from completed trials
- Members have good links with pharma, which have enabled them to have early access to new agents and this has played an important part in the Group's success.

### The Group needs to consider:

- Increasing translational science representation on the Group
- Appointing individuals with expertise in imaging, possibly interventional radiology, and histopathology
- The role that pharma may play in translational studies
- How to cognisant of and not forgetful of data from around the world when developing new studies