

**Results:** This study remains on schedule from Nov. 2009 to Mar. 2011. In 23 centers, 157 patients have been screened with 1 screen failure. Interim analysis will be done in Jun 2011, the enrollment is planned to be completed in Apr 2012. Up to now, 20 patients withdrew from the study, with 1 of capecitabine allergy, 2 of paclitaxel allergy, 4 of consent withdrawn, 2 of withdrawn after randomization, and 11 lost follow-up. Severe adverse event (SAE) is reported in 9 cases (cut-off date 31 Jan, 2011), 1 of multiorgan dysfunction syndrome (MODS), 2 of intestinal obstruction, 1 of liver dysfunction, 1 of hemorrhage, 1 of bone marrow failure, 1 of thrombosis, 1 of paclitaxel allergy, and 1 of diarrhea. One treatment-related death was suspected in all patients. Safety data is now under collection for interim safety analysis.

**Conclusion:** PX-X as first-line treatment was promising in AGC. Interim safety results and primary efficacy analysis are eagerly awaited.

## 6601

## POSTER

### Oxaliplatin, Leucovorin and Fluorouracil for Untreated Recurrent or Metastatic Esophageal Carcinoma – a Phase II Study

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**Background:** Esophageal carcinoma is one of the most common cancers, as well as one of the leading causes of cancer death in China. In Western countries, clinical trials are now primarily focusing on the treatment of adenocarcinoma, owing to the recent increase in the prevalence of this type of esophageal cancer. In China and other eastern Asian countries, squamous cell carcinoma is the main type of esophageal cancer. Monotherapy with oxaliplatin or 5-Fu has been demonstrated anticancer activity in esophageal cancer. This study was designed to evaluate the efficacy and toxicity of oxaliplatin, leucovorin and fluorouracil (FOLFOX6) in untreated recurrent or metastatic esophageal carcinoma.

**Materials and Methods:** Patients with recurrent or metastatic esophageal cancer ineligible for definitive radiotherapy were given FOLFOX6: oxaliplatin 100 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, fluorouracil (400 mg/m<sup>2</sup>) as an i.v. bolus, fluorouracil (2400 mg/m<sup>2</sup>) as a 46-h continuous infusion on day 1. Treatment cycles were administered every 14 days. The primary end point was progression-free survival (PFS). Secondary end points included objective response (OR), overall survival (OS) and safety.

Table 1. Adverse effects of 40 patients treated with FOLFOX6

Adverse effect	Number of patients				
	Total, N (%)	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	32 (80%)	10	12	8	2
Neutropenia	28 (60%)	7	9	9	3
Anemia	22 (55%)	16	3	3	1
Thrombocytopenia	11 (27.5%)	3	5	3	0
Neuropathy	25 (62.5%)	23	2	0	0
Nausea	24 (60%)	18	5	3	0
Vomiting	15 (37.5%)	12	3	0	0
Stomatitis	25 (62.5%)	21	4	0	0
Diarrhea	5 (12.5%)	5	0	0	0
Fatigue	30 (75%)	20	8	3	0
Alopecia	8 (20%)	8	0	0	0
Hyperbilirubinemia	3 (7.5%)	3	0	0	0
Elevation of AST/ALT	5 (12.5%)	5	0	0	0

**Results:** Between Oct, 2008 and Dec, 2010, a total of 40 patients with median age of 56 years old were enrolled. Baseline characteristics: male/female: 35/5; squamous/adenocarcinoma: 36/4; surgery/radiotherapy/neoadjuvant or adjuvant chemotherapy: 26/17/16; metastasis: 1 site:5 pts, 2 sites:11 pts, 3 sites:10 pts, 4 sites:12 pts, 5 sites:2 pts; mediastinal lymph node(LN) metastasis(M): 29pts, supraclavicular LN M: 21pts, retroperitoneal LN M: 17pts, liver M: 15pts, lung M: 10pts, anastomotic recurrence: 9 pts, soft tissue M: 5 pts, bone M: 5pts, gastric M: 4pts, cervical LN M: 3pts. Median cycles of FOLFOX6 were 4. PR: 17.5% (7/40), SD: 45% (18/40), PD: 32.5% (13/40), unassessable: 5% (2/40). With median follow up of 10 months, twenty-four patients died. Median PFS was 5.8 months(95% CI: 4.1–7.5). Median survival was 8.5

months (95% CI: 7.1–9.8). FOLFOX6 was well tolerated. Adverse effects were listed in table 1.

**Conclusion:** Chemotherapy with FOLFOX6 for untreated advanced esophageal cancer had promising efficacy and good tolerance. It is worthy being test further.

## 6602

## POSTER

### Immune Therapy Targeting for HER2 in Esophageal Squamous Cell Carcinoma

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**Background:** In spite of the combined modality therapy, the prognosis with advanced esophageal squamous cell carcinoma (ESCC) patients remains poor. On the other hand, cytotoxic T lymphocytes (CTL) therapy and molecular targeting therapy for HER2 were effective in a variety of tumours. These therapies are therefore an attractive approach as a novel immune-adjuvant therapy for ESCC patients. To examine the possibility of these therapies for ESCC patients, we investigated the HER2 expression in ESCC patients, the effect of molecular targeting therapy for HER2 in ESCC cell lines and MHC class I expression in ESCC patients as tumour-antigen specific CTL recognize peptide epitopes on MHC class I.

**Materials and Methods:** We assessed the HER2 expression in ESCC patients (n=85) and ESCC cell lines (n=9) by HercepTest and Fluorescence in situ hybridization (FISH). We also assessed the MHC class I expression in ESCC patients (n=80) by immunohistochemistry with anti-MHC class I monoclonal antibody. In a panel of ESCC cell lines, the effects of Herceptin and Lapatinib on anti-proliferative effect and apoptosis-inducing activity was evaluated, furthermore, the accumulation of HER2 on cell surface by Lapatinib and the combined effect of Lapatinib together with Herceptin on cell-mediated cytotoxicity were evaluated.

**Results:** In ESCC patients, FISH positive; 9.4%, HercepTest 2+/3+; 11.8% and HercepTest 1+; 17.6%. The down-regulation of MHC class I expression was observed in 38.7%, furthermore, there was a significantly inverse correlation of HER2 overexpression (FISH positive) with MHC class I expression ( $\chi^2$  test  $p=0.002$ ). One ESCC cell line expressed HercepTest 3+ and FISH positive. Herceptin and Lapatinib inhibited cell proliferation and induced apoptosis in ESCC cell lines and Lapatinib induced greater effectiveness. Lapatinib caused the surface accumulation of HER2 in all ESCC cell lines and increased Herceptin-mediated antibody-dependent cell-mediated cytotoxicity by 15–25% with 3 ESCC cell lines including a HER2-overexpressing cell line and two non-HER2-overexpressing cell lines.

**Conclusions:** Although HER2 overexpressing ESCC patients are not so good candidates for CTL therapy because HER2 overexpressing ESCC cells reduced their sensitivity for CTL by MHC class I down-regulation, Herceptin and Lapatinib have activity in HER2 expressing ESCC cells and the combination therapy of Herceptin and Lapatinib is a promising strategy in ESCC.

## 6603

## POSTER

### Prognostic Factors of 127 Patients With Advanced Small-bowel Adenocarcinoma Treated With Systemic Chemotherapy

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**Background:** No standard care has been established for advanced small-bowel adenocarcinoma (SBA). The aim of this retrospective study is to explore a most promising chemotherapy regimen for advanced SBA after adjusting the background factors by multivariate analysis.

**Methods:** The subjects were 132 patients with advanced SBA who were treated by chemotherapy. Main inclusion criteria were 1) histologically proven SBA excluding ampullary carcinoma, 2) no previous chemotherapy or radiotherapy, 3) ECOG PS 0–2. Patients were classified into the following 5 groups according to the first-line chemotherapy: A) FU alone; B) FU + CDDP; C) FU + Ox; D) FU + CPT-11; E) others. Progression free survival (PFS) and overall survival (OS) were compared with the log-rank test, and every hazard ratio (HR) was calculated using univariate and multivariate analysis with Cox's proportional hazards model.

**Results:** The number of the patients included in A), B), C), D) and E) groups was 60, 17, 22, 11 and 22. There was no significant difference in patient demographics across the treatment groups, except for PS and metastatic sites. Median PFS was A) 5.4 months, B) 3.8 months, C) 8.2 months, D) 5.6 months and E) 3.4 months. Independent predictive variables associating significantly longer PFS by multivariate analysis were: FU + Ox ( $p=0.034$ , HR=0.54, 95% CI: 0.31–0.96); good PS ( $p=0.01$ , HR=0.61, 95% CI: 0.42–0.89); absence of primary tumour ( $p=0.039$ , HR=0.65, 95% CI: 0.43–0.98); absence of target lesions ( $p=0.002$ , HR=0.43, 95% CI: 0.25–0.73). Median OS was A) 13.9 months, B) 12.6 months, C) 22.2 months, D) 9.4 months and E) 8.1 months. Predictive variables independently associated with significantly longer OS in multivariate analysis were: FU + Ox ( $p=0.022$ , HR=0.42, 95% CI: 0.20–0.88); good PS ( $p=0.018$ , HR=0.62, 95% CI: 0.42–0.92); primary site, jejunum or ileum, ( $p<0.001$ , HR=0.33, 95% CI: 0.20–0.54); undifferentiated type of histology ( $p=0.007$ , HR=0.51, 95% CI: 0.31–0.83); CEA within the normal range ( $p<0.001$ , HR=0.43, 95% CI: 0.27–0.68); CA19-9 within the normal range ( $p=0.025$ , HR=0.58, 95% CI: 0.36–0.93).

**Conclusion:** After adjusting with some other prognostic factors, FU + Ox was still a significant predictor of longer PFS and OS, suggesting that it might be a most promising first-line regimen for advanced SBA.

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POSTER

#### Updated Survival and Genomic Analysis of a Phase II Trial of Temsirolimus in Advanced Neuroendocrine Carcinomas

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**Background:** The anti-tumour activity of temsirolimus in advanced neuroendocrine carcinomas (NEC) was previously reported in a multi-center phase II trial (Duran et al. BJC 2006). Identification of prognostic or predictive biomarkers is critical to patient (pt) selection. We report the updated survival and genomic analysis for this phase II trial with more than 2 years of follow up.

**Materials and Methods:** Pts with progressive disease in the last 6 months were eligible to receive weekly temsirolimus 25 mg intravenously. 1 cycle = 4 weeks. Pts were evaluated for tumour response, time to progression (TTP) and overall survival (OS). For mutation detection, the Sequenom platform and OncoCarta Panel v1.0 were used as per protocol from Sequenom (San Diego, CA) after DNA was extracted from formalin-fixed paraffin-embedded tumour specimens.

**Results:** 37 pts were accrued between 12/2003 to 07/2005. 36 pts received a median of 4 cycles of treatment (1–44) for a total of 313 cycles of treatment. Median follow-up was 25.3 months (mo) (range 1.3–75.3 mo). 21 pts had carcinoid (C) tumours, 15 pts had islet cell carcinomas (IC). Of 33 pts evaluable for response: 3 had confirmed partial response, 20 had stable disease (12 of these were on treatment for at least 6 cycles) and 10 had progressive disease. Intent-to-treat response rate is 3/36 = 8.3%; tumour control rate is 23/36 = 63.9%. Median TTP = 5.9 mo (95% CI 3.2–16.7 mo) for the entire cohort. For the C group, median TTP = 5.9 mo (95% CI 1.7–16.7 mo); for the IC group, median TTP = 10.4 mo (95% CI 2.2–not reached) ( $p=0.70$ ). 24 pts have died. Median OS = 35.3 mo (95% CI 14.5–47.7 mo) for the entire cohort; 2 year survival = 59% (41–73%). For the C group, median OS = 47.7 mo (95% CI 7.9–69 mo); for the IC group, median OS = 35.3 mo (95% CI 14.5–39.2 mo) ( $p=0.55$ ). Genomic analysis using OncoCarta v1.0 panel was performed on 25 available tumour specimens. 1 pt had a C tumour with an AKT1-E17K mutation in 50% of the DNA sample and had a TTP of 31 mo and OS of 69 mo.

**Conclusions:** Temsirolimus appears to have persistent anti-tumour activity in NEC. An activating AKT mutation was found in 1 pt (4%) who had a prolonged TTP and OS, suggesting that AKT may possibly have predictive and/or prognostic significance in NECs (Missiaglia et al. JCO 2010).

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POSTER

#### Phase I-II Study of Radiopeptide 177 Lu-octreotate in Combination With Capecitabine and Temozolomide in Advanced Low-grade Neuroendocrine Tumours

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**Background:** Low-grade neuroendocrine tumours (NETs) arise predominantly in fore, mid and hind-gut regions and particularly gastropancreatic tissues and small-bowel. Most have somatostatin receptors which can be

targeted by octreotide and radiolabelled somatostatin analogues. Recent trials have demonstrated significant NET responsiveness to capecitabine chemotherapy either in combination with temozolomide, or with 177 Lu-octreotate.

**Methods:** All patients received a fixed activity of 7.8 GBq 177 Lu-octreotate each 8 weeks with 14 days of capecitabine 1500 mg/m<sup>2</sup> for 4 cycles. In phase I, successive cohorts of patients received escalating doses of temozolomide in groupings of 100, 150 and 200 mg/m<sup>2</sup> in the last 5 days of each capecitabine cycle. In phase II, patients were treated with 200 mg/m<sup>2</sup> temozolomide. Dose limiting toxicities, adverse events, objective tumour responses by RECIST and serum/urine NET chemistries were evaluated.

**Results:** As of January 2011, 33 patients were enrolled, 25 completed therapy and 8 ongoing. Of 25 evaluable patients: median age 63 years; primary sites: gastropancreatic 12 (48%), bowel 12 (48%), lung 1 (4%); metastatic sites: liver 21 (84%), nodal 9 (36%), other (bone 2, lung 1). Prior treatments octreotide 9 (36%), chemotherapy 4 (16%) or nil 14 (56%). Treatment was well tolerated in all dosage groups. No dose limiting grade 2, 3 or 4 toxicities were seen in cohorts 1 (100 mg/m<sup>2</sup>) or 2 (150 mg/m<sup>2</sup>). 19 patients have completed treatment at the 200 mg/m<sup>2</sup> temozolomide level; 2 patients experienced grade 3 capecitabine-induced angina, otherwise adverse events were mild to moderate. The commonest toxicities being transient nausea grade 2 (20%) and grade 3 (4%). Myelotoxicity comprised thrombocytopenia grade 2 (16%), neutropenia grade 3 (8%). There were no grade 4 events. 24 of 25 patients were evaluable for tumour response, 13 (54%) achieving partial response (PR) and 9 (38%) minor response or stable disease (SD). 2 patients progressed and have died of their disease. NET site of origin significantly influenced response, 10 of 11 (91%) gastropancreatic NETs showed PR, whilst lower rates were seen with small-bowel 3 PR (25%) and 8 SD (67%).

**Conclusion:** 177 Lu-octreotate in combination with capecitabine 1500 mg/m<sup>2</sup> for 14 days and temozolomide 200 mg/m<sup>2</sup> for 5 days given each 8 weeks for 4 cycles is well tolerated in patients with advanced, progressive, low-grade NETs and achieves high overall tumour control rates.

This trial was approved by the Fremantle Hospital Human Rights and Ethics Committee and registered with the Australian Clinical Trial Registry: ACTRN 12610000440022.

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POSTER

#### Frequency and Prognostic Value of KIT and PDGFRα Mutations in GIST From Russian Patients

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**Background:** Activating mutations in KIT and PDGFR-α tyrosine kinases are central to the pathogenesis of gastrointestinal stromal tumours (GISTs) and are associated with different clinical behaviour. Aim of the study was to analyze mutations in KIT or PDGFRα in GISTs from Russian patients and estimate their prognostic value.

**Methods:** We have analysed DNA samples obtained by microdissection of tumour cells from paraffin sections of 203 GISTs patients. Mutations in KIT (exons 9, 11, 13, 17) and PDGFRα (exons 12, 14 and 18) were studied with PCR followed with direct sequencing.

**Results:** Females represented 61% of GISTs in our series. 96% of GISTs were CD117 positive. 76.4% of GISTs harbor KIT mutations, of them 65.6% were located in exon 11 and 9.3% in exon 9. Mutations in KIT exons 13 and 17 were rare. Mutations in PDGFRα were found in 11.8% of GISTs, of them 10.3% in exon 18 and 1.5% in exon 12. Typical substitution D842V was found in 8 GISTs (4%), while deletions and other missense mutations were predominated. 12.8% GISTs had wild type KIT and PDGFRα, of them three young women had Carney triad and one man had gastric GIST with neurofibromatosis. There were also four pediatric GISTs with wild type KIT and PDGFRα and one case with KIT mutation. Patients with PDGFRα mutations or wild type GIST had significantly better survival than ones with KIT mutations. The higher overall survival prior to target therapy was shown for patients with duplication or point mutations in KIT exon 11 in comparison to exon 11 deletions. Significant difference in survival was found between GIST patients with deletions in 5'-end of KIT exon 11 (K550-I563) and deletions of main autophosphorylation sites (Y568, Y570). Among 15 GISTs with duplications in 3'-end of KIT exon 11 there were men of 40–60 years besides women over age 65. Duplications in KIT exon 9 (A502-Y503) were found in aggressive intestinal GISTs and in one gastric GIST with moderate malignancy. Several mutations in KIT and PDGFRα have not been reported in GISTs before.

**Conclusions:** The analysis of KIT and PDGFRα mutations in Russian patients has revealed some differences in frequency of specific mutations.