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.

6604 POSTER

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

N.G. Chau[1], S. Kamel-Reid[1], T. Zhang[1], H. Kindler[2], L. Saltz[3], H. Hirte[1], W. Kocha[1], G. Goss[1], L. Wang[1], L.L. Siu[1]. *[1]Princess Margaret Hospital Phase II Consortium, Princess Margaret Hospital Phase II Consortium, Toronto, Canada; [2]University of Chicago Medical Center, Department of Hematology and Oncology, Chicago, USA; [3]Memorial Sloan-Kettering Cancer Center, Gastrointestinal Oncology, New York, USA*

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).

6605 POSTER

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

P. Claringbold[1], P. Brayshaw[2], R. Price[3], J.H. Turner[2]. *[1]Fremantle Hospital, Oncology, Fremantle, Australia; [2]Fremantle Hospital, Nuclear Medicine, Fremantle, Australia; [3]Fremantle Hospital, Radiology, Fremantle, Australia*

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^2 for 4 cycles. In phase I, successive cohorts of patients received escalating doses of temozolomide in groupings of 100, 150 and 200 mg/m^2 in the last 5 days of each capecitabine cycle. In phase II, patients were treated with 200 mg/m^2 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^2) or 2 (150 mg/m^2). 19 patients have completed treatment at the 200 mg/m^2 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^2 for 14 days and temozolomide 200 mg/m^2 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.

6606 POSTER

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

I. Tsyganova[1], I.S. Beliakov[1], I.M. Gagarin[1], V.V. Mochalnikova[2], P.P. Arhiry[3], M.P. Nikulin[3], O.A. Anurova[2], N.N. Mazurenko[1]. *[1]Blokhin Cancer Research Center, of Oncogenomics, Moscow, Russian Federation; [2]Blokhin Cancer Research Center, of Pathology, Moscow, Russian Federation; [3]Blokhin Cancer Research Center, of Abdominal Oncology, Moscow, Russian Federation*

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 *PDGRFA* (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 *PDGRFA* 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 missence mutations were predominated. 12.8% GISTs had wild type *KIT* and *PDGFRA*, 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 *PDGFRA* and one case with *KIT* mutation. Patients with *PDGFRA* mutations or wild type GIST had significantly better survival then 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 *PDGFRA* have not been reported in GISTs before.
Conclusions: The analysis of *KIT* and *PDGFRA* mutations in Russian patients has revealed some differences in frequency of specific mutations.

We are sure that type of mutation significantly influenced GIST prognosis and mutations should be analyzed before adjuvant therapy.

6607 POSTER

Description of Mutation in CNR1 Gene and VEGF Expression in Esophageal Cancer

J.C. Meneu-Diaz[1], F. Bedoya[2], R. Enriquez -Salamanca[2], I. Vegh[2], A. Moreno Elola-Olaso[3], A. Marcacuzco[4], P. Rico-Selas[4], A. Moreno[4]. *[1]Hospital 12 de Octubre, Upper GI Unit, Madrid, Spain; [2]Hospital 12 de Octubre, Research Unit, Madrid, Spain; [3]Westchester Medical Center, Minimally Invasive Unit, New York, USA; [4]Hospital 12 de Octubre, Upper GI Unit, Madrid, Spain*

Aims and Background: Cannabinoid receptors have an impact on gastrointestinal function, but it remains unknown whether mutations may affect tumour susceptibility in patients with esophageal carcinoma. The aim of this study was to determine mutation in the cannabinoid receptor-1 (CNR1) gene and its relation to vascular endothelial growth factor (VEGF) expression as an angiogenic and poor prognostic factor.
Methods: 179 esophageal tissue samples from 69 patients (29 with esophageal cancer and 40 controls) were studied. CNR1 gene mutation (1359 G $\rightarrow$ A in codon 453) was detected with PCR, using the MspI restriction enzyme. VEGF was determined by immunoassay.
Results: Genotyping in control patients' samples revealed that 24/40 were G/G wild type and 16/40 were G/A; no samples were A/A. Of the 139 tissue samples from the 29 esophageal cancer patients, 15 were G/G homozygous, 85 G/A heterozygous, 11 had an A/A genotype and 28 were without amplification. In the normal tissue adjacent to tumour, some mutations were observed. The overall survival time was reduced in patients with the A/A type in all their 5 samples, in comparison to G/G type ($P = 0.04$, chi-square: 4.26). VEGF expression was higher in tumour than nontumour areas ($P < 0.025$). VEGF expression was not correlated with survival time.
Conclusions: Our preliminary findings in esophageal tissue showed a high frequency of G $\rightarrow$ A mutation in the CNR1 gene. No correlation between VEGF expression and gene receptor mutation was found. Patients with mutation in all their samples had a reduced survival time.

6608 POSTER

Bax and p53 as Outcome Predictive in Metastatic Gastric Cancer (MGC) Patients Treated With First-Line COI (Capecitabine, Oxaliplatin, and Irinotecan) Regimen

F. Pietrantonio[1], P. Biondani[1], A. Pellegrinelli[2], V. Colonna[1], G. Bianchini[1], K.F. Dotti[1], L.E. Franceschelli[1], R. Buzzoni[1], M. Di Bartolomeo[1]. *[1]Fondazione IRCCS Istituto Nazionale Tumori, Medical Oncology, Milano, Italy; [2]Fondazione IRCCS Istituto Nazionale Tumori, Pathology Department, Milano, Italy*

Background: Bax plays a central role in apoptosis signalling and might be a chemosensitivity biomarker. P53 is a gene regulator of Bax, but its significativity as independent biomarker is controversial. Poorer survival for localised tumours harbouring double alteration of Bax and p53 was previously reported, although only Bax was an independent prognosticator *(Mrózek, 2003*). The aim of this retrospective study was to investigate the predictive/prognostic value of Bax/p53 in mGC pts homogeneously treated with a oxaliplatin-containing regimen.
Methods: First-line treatment with COI (capecitabine 1000 mg/m^2 twice daily d2−6; oxaliplatin 85 mg/m^2 d2; irinotecan 180 mg/m^2 d1; biweekly schedule) was administered to a consecutive series of mGC pts for up to 8 cycles, or until progressive disease (PD)/unacceptable toxicity. Performance status (PS) $\leqslant 1$: eligibility criteria to triplet chemotherapy. Tissue blocks available for 23 pts who provided written consent. Bax/p53 expression assessed by immunohistochemistry, with dicotomic discrimination. Association of both biomarkers with RECIST response by two tailed Fisher's exact test. Correlation of Bax/p53 and PS with progression-free (PFS) and overall (OS) survival by univariate and multivariate Cox's proportional hazard model.
Results: Two pts not evaluable by RECIST criteria. Overall, 71% response rate (15/21, 11 PR/4 CR). Bax-positive was documented in 74% (17/23) samples and negative in 26% (6/23); p53 negative in 61% (14/23) and overexpressed in 39% (9/23). Response rate was 87% (13/15) in Bax-positive and 33% (2/6) in BAX-negative ($p = 0.03$). By Cox univariate analysis, Bax negative tumours showed a statistically significant shorter PFS (3.9 vs 7.4 mos; HR = 3.40, CI 1.17–9.93; $p = 0.02$) and OS ($p = 0.04$). In multivariate analysis for Bax and PS, Bax-negative tumours showed a significantly higher risk for progression (HR 4.51, CI 1.30–15.6; $p = 0.02$) and death (HR 6.69, CI 1.30–15.6; $p = 0.01$); and sub-optimal PS (ECOG 1) was associated with a trend for worst overall survival ($p = 0.08$). p53 evaluation failed to show any significant correlation with outcome.
Conclusions: In mGC pts selected for good-intermediate PS, Bax expression is associated with higher responses to first-line COI regimen. Bax negative pts showed poorer outcome, while p53 overexpression did not have an impact on disease prognosis. Prospective confirmation of predictive/prognostic role of Bax in mGC treated with specific chemotherapeutic drugs is warranted.

6609 POSTER

RON (MST1R) is a Novel Therapeutic Target for Gastroesophageal Adenocarcinoma

D. Catenacci[1], L. Henderson[1], M. Tretiakova[2], T. Karrison[3], R. Salgia[1]. *[1]University of Chicago, Medicine, Hematology/Oncology, Chicago, USA; [2]University of Chicago, Pathology, Chicago, USA; [3]University of Chicago, Department of Health Studies and Biostatistics, Chicago, USA*

Background: RON (MST1R) is a member of the MET receptor tyrosine kinase family with a putative role in cancer, and we have recently described its expression and function in human tissues and *in vitro* in gastroesophageal cancer (GEC) (AACR 2011, LB-124, Catenacci et al; in press); here we further describe the role of RON expression and therapeutic potential in a murine model, with focus on RON and MET signaling synergy and redundancy as a mechanism of resistance to individual receptor inhibition.
Methods: To confirm our *in vitro* findings, we assessed the function of RON in a GEC cell line, AGS, in a subcutaneous nude mouse model. GEC cell line growth inhibition was evaluated using RON specific novel monoclonal blocking antibodies, small molecule tyrosine kinase inhibitors and a RON shRNA AGS line. We used immunohistochemistry (IHC), immunoblotting (IB), and fluorescence in situ hybridization (FISH) to evaluate RON and MET expression, activation, and copy number in harvested treated tumours and controls to evaluate for mechanisms of resistance. We assessed RON and/or MET inhibition in order to evaluate for inhibitory synergism as a result of RON and MET functional reciprocity and signaling redundancy as we recently described *in vitro*.
Results: Tumour take rate was significantly inhibited with RON knockdown in the shRON AGS line versus scrambled control ($p < 0.01$). Those shRON tumours that did take occurred significantly later than control − with some revealing increased MET expression and others through selection of a RON re-expressing clone. shRON tumours were significantly less vascular as assessed grossly and by anti-CD31 IHC. shRON tumour growth rate was significantly less than the scrambled AGS control ($p < 0.01$). RON and MET simultaneous inhibition with monoclonal antibodies or small molecules resulted in a lower tumour take rate and growth rate than with inhibition of either receptor alone or negative controls.
Conclusions: RON protein knockdown and inhibition with antibodies and small molecules significantly decreased the ability of tumours to take, with less tumour vasculature providing a possible downstream mechanism of action. This suggests a role for neoadjuvant/adjuvant anti-RON treatment of GEC in the peri-operative setting to improve disease-free survival, as well as in the advanced metastatic setting given the observed tumour growth inhibition. RON and MET co-inhibition led to optimal results, confirming our previous *in vitro* observations. These studies further define RON as an important novel therapeutic target for GEC, and supports continued investigation of its role and development of RON specific inhibitors for this deadly disease.

6610 POSTER

The Significance of the Changing of Serum M30 and M65 Values After Chemotherapy and Relationship Between These Values and Clinicopathological Factors in Patients With Advanced Gastric Cancer

A. Bilici[1], B.B. Oven Ustaalioglu[1], S. Ercan[2], A. Orcun[2], M. Seker[1], T. Salepci[1], M. Gumus[1]. *[1]Dr. Lutfi Kirdar Kartal Education and Research Hospital, Department of Medical Oncology, Istanbul, Turkey; [2]Dr. Lutfi Kirdar Kartal Education and Research Hospital, Department of Biochemistry, Istanbul, Turkey*

Background: M30 and M65 are intact forms of cytokeratin 18 and, they release during apoptotic cell death from the epithelial cells. In some studies, prognostic importance and predictive significance to detect response to chemotherapy of M30 and M65 values have been reported. In the present study, we aimed to determine the changing of serum M30 and M65 values after chemotherapy and the impact of these values on treatment response and progression-free (PFS) and overall survival (OS) of patients with advanced gastric cancer.
Material and Methods: A total of thirty-one patients with advanced gastric cancer were included. M30 and M65 values were measured by quantitative ELISA method in serum samples before and 48 hours after first chemotherapy cycle. Pre- and postchemotherapy values of M30 and