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

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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).

6605 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^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

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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 *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.