Results: Median age at diagnosis was 61 years (range 33 to 88), 67.6% were male, 86.4% had ECOG 0 or 1, 64.8% tumours were intrahepatic, 24.3% were from gallbladder and 10.8% were Klatskin carcinomas. According to tumour grading, 18.9% were well differentiated, 35.1% were moderately differentiated, 24.3% were poorly differentiated and 21.6% was not informed. All 37 patients were recommended palliative systemic therapy as primary treatment with cisplatin (or oxaliplatin) plus gemcitabine regimen until progression or death. Cetuximab was added to the chemotherapy regimen of 13 patients since May 2009. Overall, 28 (75.6%) patients were followed until death with a median follow-up of 9.2 month. Nine (24.3%) patients are still on therapy, 8 of them are still using cetuximab containing therapy, with a median follow-up of 24.4 months. The median overall survival of patients receiving cetuximab was not reached and it is significantly longer than the median overall survival of patients who never received cetuximab (9.2 months; 95% CI 3.5–12.3) (p = 0.0105, two sided log rank test).
Conclusions: In this retrospective analysis, the introduction of cetuximab in combination with cisplatin-containing chemotherapy regimens seems to improve survival of patients diagnosed with advanced carcinoma of the biliary tract. The completed randomized phase II trial may confirm the precise role of cetuximab in this disease once data is available. Due to rarity of this patient population and limitations of efficacy of current therapies, patients' referral to prospective phase III trials should be a high priority.

6560 POSTER

A Phase I Safety and Pharmacokinetic Study of Everolimus, an Oral mTOR Inhibitor, in Subjects With Impaired Hepatic Function

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Background: Everolimus, an oral mTOR inhibitor that demonstrates effective antitumour activity in several human tumours, is metabolized through the hepatic CYP450 pathway. Everolimus safety and pharmacokinetics (PK) in the setting of mild to severe hepatic impairment (Child-Pugh A, B, and C, respectively) has not been reported. This study assessed PK and safety of everolimus in pts with different degrees of hepatic impairment. The relationship between PK parameters and hepatic function was also investigated.
Materials and Methods: (ClinicalTrials.gov NCT00968591) Pts $\geqslant$18 years of age were assigned to 1 of 4 treatment groups: group 1 (normal hepatic function); group 2 (Child-Pugh A; score 5−6); group 3 (Child-Pugh B; score 7−9), or group 4 (Child-Pugh C; score 10−15). Pts received a single 10-mg dose of everolimus after a low-fat breakfast. PK parameters were determined by a validated noncompartmental analysis method using WinNonlin® Pro (Version 5.2).
Results: 34 pts (group 1, n = 13; group 2, n = 7; group 3, n = 8; group 4, n = 6) were evaluable for PK and safety. Baseline demographics were similar across groups (median age 44 years, male 79.4%, white 91.2%). Mean C_{max} and t_{max} of everolimus were comparable between normal or hepatic-impaired pts. Postabsorption-phase kinetics were notably different in normal vs hepatic-impaired pts. Compared to normal controls, there was a 1.6-fold, 3.26-fold, and 3.64-fold increase in everolimus $AUC_{(0-inf)}$ for patients with mild, moderate, and severe hepatic impairment, respectively. Everolimus $AUC_{(0-inf)}$ correlated positively with bilirubin level ($r^2 = 0.54$) and INR ($r^2 = 0.65$); a negative correlation was observed with albumin ($r^2 = 0.56$). Post hoc analysis suggested dose adjustment based on bilirubin or albumin may result in over- and underdosing. Incidence of AEs was higher in groups 3 (n = 3) and 4 (n = 2) than in the control (n = 1) and group 1 (n = 1). The majority of AEs were grade 1 severity, $\leqslant$1 day in duration, and not everolimus related.
Conclusion: Hepatic impairment assessed by Child-Pugh class correlates with everolimus PK and should be used to guide dose adjustment in pts with hepatic impairment. For pts with mild or moderate hepatic impairment, the recommended starting dose of everolimus is 7.5 mg and 2.5 mg OD, respectively. Everolimus cannot be recommended for pts with severe hepatic impairment (Child-Pugh C) unless in the best interest of the pt; a starting dose of 2.5 mg OD must not be exceeded. Safety of everolimus was consistent with previous experience.

6561 POSTER

Updated Survival and Safety Data From RADIANT-3 − a Randomized, Double-blind, Placebo-controlled, Multicenter, Phase III Trial of Everolimus in Patients With Advanced Pancreatic Neuroendocrine Tumours (pNET)

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Background: Effective treatments for controlling disease progression in pts with advanced pNET are limited. Estimated median overall survival (OS) for treatment-naive pts with metastatic disease is 24 mo (Yao et al, 2008). In the largest randomized phase III study (RADIANT-3, NCT 00510068) in pts with advanced pNET, everolimus, an oral mTOR inhibitor, provided a statistically significant 2.4-fold improvement in progression-free survival (PFS) vs placebo (HR, 0.35; 95% CI, 0.27–0.45; $P < 0.0001$). Here we present an update of the survival and safety analysis from this trial.
Materials and Methods: Pts with progressive advanced low- or intermediate-grade pNET were randomly assigned to everolimus 10 mg/d orally (n = 207) or placebo (n = 203); both arms received best supportive care. Primary endpoint was PFS (RECIST v1.0). Upon disease progression, pts assigned to placebo could cross over to open-label everolimus. The updated OS analysis cutoff date was Feb 23, 2011 (143 events: 68 everolimus; 78 placebo). Adverse events (AEs) were coded to a preferred term and graded using the National Cancer Institute Common Toxicity Criteria (v3.0). The safety population included 407 pts (204 everolimus; 203 placebo).
Results: Of the 203 placebo pts, 172 (85%) crossed over to open-label everolimus; 124 of the 146 (58%) pts with disease progression crossed over to open-label everolimus during blinded study therapy. Median OS was 36.6 mo in the placebo arm and has not been reached in the everolimus arm (HR, 0.89; 95% CI, 0.64–1.23). Median PFS for pts who received open-label everolimus after disease progression was 11.43 mo. Median safety follow-up now extends to 20.1 mo. Most common drug-related AEs with everolimus vs placebo remained stomatitis (52.9% vs 12.3%), rash (48.5% vs 10.3%), and diarrhea (34.3% vs 10.3%). Anemia (5.9% vs 0%), hyperglycemia (5.9% vs 2.5%), and stomatitis (4.9% vs 0) were the most common drug-related grade 3/4 events for everolimus and placebo, respectively.
Conclusions: At 40 mo of follow-up, the median OS has not been reached in the everolimus arm. Median OS in the placebo arm, in which substantial crossover occurred benefitting these patients, exceeds the median previously observed for pts with metastatic pNET. The safety of everolimus observed in this analysis was consistent with previous experience. Final survival analysis will be completed after 282 events.
Study supported by Novartis.

6562 POSTER

Perioperative Chemotherapy in Resectable Gastric Cancer − a Single Centre Review

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Background and Objective: Perioperative chemotherapy (CHT) with epirubicin, cisplatin and infusional fluorouracil (ECF) has shown benefits in resectable gastric cancer, improving progression-free and overall survival. We reviewed the feasibility of perioperative CHT in our setting, as for the completion of the protocol and tolerability.
Material and Methods: Patients (pts) clinical files with gastric or gastroesophageal junction cancer submitted to perioperative CHT were reviewed from January 2009 to October 2010.
Results: Forty-two (pts) were treated, 33 male and 9 female, with a medium age of 66 years. The histological diagnosis was adenocarcinoma, with 2 cases of signet ring cells carcinoma and 8 cases of mucinous adenocarcinoma. All tumours were T $\geqslant$ 3 or N positive. Chemotherapy was based in ECF. In 10 pts, cisplatin was replaced for oxaliplatin due to polyneuropathy (1 pt), cardiac disease (6 pts) and hearing problems (1 pt). In 1 pt, fluorouracil was replaced for capecitabine due to catheter complications and in another patient epirubicin was