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

J. Peveling-Oberhag[1], S. Zeuzem[1], W.P. Yong[2], T. Kunz[3], T. Paquet[4], E. Bouillaud[4], S. Urva[3], O. Anak[4], D. Sellami[3], Z. Kobalava[5]. *[1]Klinik der J.W. Goethe Universität, Department of Medicine, Frankfurt/Main, Germany; [2]National University Cancer Institute, Oncology, Singapore, Singapore; [3]Novartis Pharmaceuticals, N/A, Florham Park NJ, USA; [4]Novartis Pharma AG, N/A, Basel, Switzerland; [5]Peoples Friendship University of Russia, Center of Applied Clinical Pharmacology, Moscow, Russian Federation*

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)

C. Lombard-Bohas[1], E. Van Cutsem[2], J. Capdevila[3], E.G.E. de Vries[4], P. Tomassetti[5], J. Lincy[6], R.E. Winkler[7], T. Hobday[8], R. Pommier[9], J.C. Yao[10]. *[1]Hopital Edouard Herriot, Lyon, France; [2]University Hospital Gasthuisberg/Leuven, Digestive Oncology Unit, Leuven, Belgium; [3]Vall d'Hebron University Hospital, Medical Oncology, Barcelona, Spain; [4]University Medical Center, Medical Oncology, Groningen, The Netherlands; [5]University Hospital St. Orsola, Bologna, Italy; [6]Novartis Pharma, Oncology, Basel, Switzerland; [7]Novartis Pharmaceuticals Corporation, Oncology, Florham Park, USA; [8]Mayo Clinic, Breast and Oncology, Rochester, USA; [9]Oregon Health and Science University, Surgical Oncology, Portland, USA; [10]University of Texas MD Anderson Cancer Center, Gastrointestinal Medical Oncology, Houston, USA*

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

A. Clara[1], T. Alexandre[1], A. Luís[1], J. Freire[1], J. Oliveira[1]. *[1]Instituto Portugues Oncologia, Oncologia Medica, Lisboa, Portugal*

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

omitted because of compromised LEVF. Twenty six pts completed all protocol treatments (chemotherapy and surgery). Forty-one pts completed preoperative chemotherapy and underwent surgery. In 5 pts surgery was palliative, for unresectable or unsuspected metastatic disease. Reasons for not completing treatment were: disease progression (10 pts), postoperative complications (3 pts), prolonged neutropenia (1 pt), febrile neutropenia with septic shock and prolonged UCI stay (1 pt) and diverticulitis (1 pt). Dose reduction was required in 9 pts, due to diarrhea (3 pts), neutropenia (2 pts), neurotoxicity (1 pt), weight loss (1 pt), catheter complications (2 pt). Chemotherapy delay occurred in 23 pts (minimum 7 days − maximum 14 days), and the main causes were: delay in admission, neutropenia, diarrhea, and postoperative complication. With a medium follow up of 37 months, 7 pts died of progressive disease, two of them had completed full treatment.
Conclusion: Completion of all planned perioperative chemotherapy was observed in 71% of patients. Disease progression was the main reason to stop chemotherapy and although some pts were not able to receive post-operative treatment, tolerability was reasonable.

6563 POSTER

Chromogranine a (CG-A) Plus Vascular Endothelial Growth Factor (VEGF) as Predicting Factors (PF) of Sorafenib (SFB) Treatment of Multifocal Hepatocellular Carcinoma (M-HCC) in Elderly Patients

M. Antista[1], F. Bellomo[1], G. Pernice[1], I. Carreca[1]. [1]*A.O.U.P. Paolo Giaccone, Chair of Medical Oncology Oncogeriatric Unit School of Medicine, Palermo, Italy*

Background: To date HCC accounts for approximately 90% of all primary liver cancers, this is the fifth most common cancer in the world with very poor prognosis. Despite treatment M-HCC outcomes are very discouraging and only sorafenib one of new TKI has demonstrated better effectiveness. Furthermore, till now we can only monitoring therapy effectiveness and prognosis with CT-Scan or Liver-Sonography or MRI.
Based on preliminary findings, authors will investigate if Cg-A and VEGF work as predicting factors of Sorafenib treatment's outcomes.
Material and Methods: 27 patients, mean age 68.6 (65−85) with M-HCC were observed and enrolled in this study in the last 24 months. Serum Cg-A (Chromogranin A ELISA), VEGF (Human VEGF ELISA) and αFP were evaluated at baseline and after end of treatment. SFB was delivered at standard dose of 400 mg p.o. bid and no one patients discontinued treatment for HFS and G.I.tract toxicity. Clinical response (RECIST), Comprehensive Geriatric Assessment and PFS were considered as well.
Results: Cg-A mean value was: (baseline) 78.7±9.0 ng/ml (after treatment) 25.59±9.0 ng/ml. VEGF levels was: (baseline) 65.8±8.7 pg/ml (after treatment) 48.33±8.7 pg/ml. Hand-Foot Syndrome and G.I. tract toxicity (grade 3−4) was not observed in these pts. Clinical benefit correlated with lower values of CgA and VEGF.
Conclusions: Both Cg-A and VEGF seem to be in reciprocal relation with response to SFB therapy in elderly with M-HCC patients. Further, a correlation between CT-Scan, Sonography and MRI of liver with prognosis of M-HCC was shown. A large number of patients are enrolling to convalidate these findings.

6564 POSTER

Correlation of PFS With Early Response of Chromogranin A and 5-hydroxyindoleacetic Acid Levels in Pts With Advanced Neuroendocrine Tumours: Phase III RADIANT-2 Study Results

E. Baudin[1], E. Wolin[2], D. Castellano[3], G. Kaltsas[4], A. Panneerselvam[5], Z. Tsuchihashi[6], S. Saletan[7], J.C. Yao[8], D. Gross[9]. [1]*Institut Gustave-Roussy, Department of Nuclear Medicine, Villejuif, France;* [2]*Cedars-Sinai Medical Center Medicine, Medical Oncology, Los Angeles, USA;* [3]*University Hospital 12 de Octubre, Medical Oncology, Madrid, Spain;* [4]*University of Athens, Pathophysiology, Athens, Greece;* [5]*Novartis Pharmaceuticals Corporation, Oncology Biometrics and Data Management, Florham Park, USA;* [6]*Novartis Pharmaceuticals Corporation, Oncology Biomarkers and Clinical Imaging, Florham Park, USA;* [7]*Novartis Pharmaceuticals Corporation, Oncology, Florham Park, USA;* [8]*University of Texas MD Anderson Cancer Center, Gastrointestinal Medical Oncology, Houston, USA;* [9]*Hadassah-Hebrew University Medical Center, Neuroendocrine Tumour Unit, Jerusalem, Israel*

Background: In the phase III RADIANT-2 trial (NCT00412061; ESMO 2010 Abstract LBA8), everolimus 10 mg/d, an oral mTOR inhibitor, + octreotide LAR 30 mg IM q28 days (E+O) demonstrated a clinically meaningful 5.1-mo increase in median progression-free survival (PFS) compared with placebo + octreotide LAR (P+O) in pts with low- or intermediate-grade advanced NET and a history of flushing and diarrhea. Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are important biomarkers of tumour burden and carcinoid syndrome in NET. Elevated vs nonelevated baseline CgA (11.3 vs 26.8 mo; HR, 0.45; $P < 0.001$) and 5-HIAA (13.6 vs 15.4 mo; HR, 0.79; $P = 0.130$) have been shown to be associated with shorter median PFS (WCGI 2011). This analysis examined the effect of baseline and early CgA and 5-HIAA response on PFS in the RADIANT-2 trial.
Materials and Methods: Pts with low- or intermediate-grade advanced NET were randomly assigned to E+O (n = 216) or P+O (n = 213). Primary endpoint was PFS (RECIST v1.0). Serum CgA and 24-h urinary 5-HIAA were collected at baseline and on day 1 of each cycle. Early CgA and 5-HIAA responses, defined as ⩾50% reductions at week 4, were correlated with PFS using a Cox-proportional hazards model.
Results: At baseline, 71.7% of E+O pts and 62.5% of P+O pts had elevated CgA (>2×ULN); elevated (>2×ULN) 5-HIAA was observed in 67.9% and 66.0%, respectively. The number of pts with early CgA (24.5% vs 16.5%) and 5-HIAA (24.0% vs 17.5%) responses were greater with E+O than P+O. Median PFS was significantly longer among pts with an early CgA response (27.3 vs 10.6 mo; HR, 0.35; $P < 0.001$) vs those without early response, regardless of treatment. Patients with early 5-HIAA response also had a longer median PFS than those without, but it did not reach statistical significance (18.3 vs 13.6 mo; HR, 0.71; $P = 0.139$).
Conclusions: In the large population of pts from the phase III RADIANT-2 trial, early CgA responses were associated with significantly improved PFS regardless of treatment, suggesting that early CgA response may serve as a surrogate for favorable PFS.
Study supported by Novartis.

Early response	Median PFS		Hazard Ratio	*P*
	E+O (N = 216)	P+O (N = 213)	E+O vs P+O	
CgA				
Yes	27.3 (13.9, NR) n = 34	27.8 (13.0, 30.4) n = 20	0.79 (0.4, 1.8)	0.283
No	13.7 (10.6, 16.1) n = 105	8.3 (5.9, 9.4) n = 101	0.54 (0.4, 0.8)	<0.001
5-HIAA				
Yes	18.3 (8.57, NR) n = 24	16.9 (8.4, 30.4) n = 18	0.81 (0.4, 1.8)	0.229
No	18.6 (13.6, 24.8) n = 76	8.4 (8.1, 13.6) n = 85	0.54 (0.3, 0.8)	0.003

NR, not reached.

6565 POSTER

Androgens in the Etiology of Esophageal Adenocarcinoma − a Population-based Cohort Study on Prostate Cancer Patients in Sweden 1961 to 2008

R. Shore[1], R. Ljung[1], F. Mattsson[1], J. Lagergren[1], M. Lindblad[1]. [1]*Karolinska Institutet, MMK UGIR, Solna Stockholm, Sweden*

Background: The incidence of esophageal adenocarcinoma is continuing to rise in western populations. There is a major male predominance, unexplained by sex differences in the distribution of known risk factors. Androgens may play a role in the etiology of esophageal adenocarcinoma and anti-androgen treatment might thus protect against the development of this tumour.
Material and Methods: The nationwide Swedish Cancer Register was used to identify a cohort of men diagnosed with a first malignant primary of prostate cancer, an androgen sensitive tumour often receiving hormonal therapy. All participants in the cohort were followed until a diagnosis of a second primary cancer, death, loss to follow-up or end of the study period. Age- and period adjusted standardized incidence ratios (SIR) with 95% confidence interval (CI) were calculated as an estimation of relative risk for a second malignant primary tumour of the esophagus.
Results: Between 1961 and 2008 190,497 patients developed cancer of the prostate as a primary malignant tumour in Sweden. Following exclusion for a follow-up period of less than one year 162,771 patients were eligible for study, contributing 712,496 person-years of follow-up. In total, 60 primary esophageal adenocarcinoma were observed in the cohort as compared to 62.1 expected, resulting in a SIR of 0.97 (95% CI 0.74−1.24).
Conclusions: The risk of developing esophageal adenocarcinoma following a diagnosis and treatment of a primary prostate cancer was no different than expected in the general population. Despite a large cohort our study was hampered by a small number of cases of esophageal adenocarcinoma and of misclassification of anti-androgen exposure diluting