progressing advanced NET who were SSA-naive had longer median PFS when treated with octreotide LAR alone compared to patients who had prior SSA, supporting the antitumour effects of octreotide LAR demonstrated in the PROMID trial.
Study supported by Novartis.

**6572** POSTER

**Effect of Everolimus + Octreotide LAR in Patients With Advanced Lung Neuroendocrine Tumours − Analysis From RADIANT-2**

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**Background:** The lung is the second most common site of occurrence of neuroendocrine tumours (NET). No approved antitumour agents are available for the treatment of lung NET. An antitumour effect of everolimus, an oral mTOR inhibitor, in human bronchial carcinoid tumour cells in vitro has been reported. In the RADIANT-2 trial (NCT00412061; ESMO 2010 Abstract LBA8), everolimus plus octreotide LAR (E+O) provided a clinically meaningful 5.1-mo prolongation of median progression-free survival (16.4 mo E+O vs 11.3 P+O; HR, 0.77; 95% CI, 0.59–1.00; $P = 0.026$) vs placebo plus octreotide LAR (P+O) in pts with advanced NET and a history of flushing or diarrhea. Exploratory analysis of PFS by tumour site demonstrated that E+O was beneficial across all primary tumour site patient subgroups, including lung NET. An analysis of pts with lung NET and their response to E+O is presented.
**Materials and Methods:** 429 pts (ITT population) with low- or intermediate-grade advanced NET were randomly assigned to either everolimus 10 mg/d plus octreotide LAR 30 mg intramuscularly q28d (n = 216) or placebo plus octreotide LAR (n = 213). The primary endpoint was PFS per central review (RECIST v1.0). Baseline demographics, disease characteristics, biomarker levels, and tumour response to treatment were analyzed for the subset of pts with lung NET.
**Results:** 44 pts with lung NET were identified: 33 in the everolimus arm and 11 in the placebo arm. Baseline demographics and disease characteristics of lung NET pts were similar to those of the overall patient population. Among the lung NET pts, a higher proportion of pts receiving E+O vs P+O were >65 years (42% vs 18%), were diagnosed $\geqslant$2 years earlier (76% vs 55%), and had elevated baseline CgA (>2 $\times$ ULN) and 5-HIAA (>median) (52% vs 36%). Median PFS for pts with lung NET was 13.63 mo in the E+O group vs 5.59 mo in the P+O group (HR, 0.72; 95% CI, 0.31–1.68; $P = 0.228$). More E+O than P+O lung NET pts experienced some degree of tumour shrinkage consistent with the findings in the overall study population (67% vs 27% for lung NET, 75% vs 45% for overall population).
**Conclusions:** Everolimus plus octreotide LAR improved PFS in pts with advanced low-/intermediate-grade lung NET similar the overall population despite the poor prognosis of these pts. The imbalance in the frequency of this important baseline prognostic factor favoring the P+O arm should be considered when interpreting the overall results of the trial.
Study supported by Novartis.

**6573** POSTER

**Effect of Everolimus Treatment on Markers of Angiogenesis in Patients With Advanced Pancreatic Neuroendocrine Tumours (pNET) − Results From the Phase III RADIANT-3 Study**

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**Background:** The mammalian target of rapamycin (mTOR) is a cytoplasmic protein kinase that regulates cellular metabolism, growth, proliferation, and angiogenesis. Inhibition of mTOR is thought to inhibit angiogenesis through a mechanism distinct from VEGF inhibitors and has been shown to reduce endothelial cell proliferation in vitro and tumour vascularization in vivo. In the RADIANT-3 trial (NCT00428597), everolimus, an oral inhibitor of mTOR, significantly prolonged progression-free survival (PFS) in patients with advanced pNET (Yao et al., NEJM, 2011). We determined the effects of everolimus treatment on levels of several angiogenic biomarkers in patients in the RADIANT-3 trial.
**Materials and Methods:** Patients with progressive, advanced low- or intermediate-grade pNET were randomly assigned to everolimus 10 mg/d orally (n = 207) or placebo (n = 203). Serum samples were collected and analyzed for VEGF, PLGF, bFGF, sVEGFR1, and sVEGFR2 at baseline and on day 1 of cycles 2 through 4. Treatment effect on change from baseline over time was analyzed using a repeated-measures model adjusting for other prognostic factors.
**Results:** Everolimus vs placebo resulted in a significant reduction of sVEGFR2 ($P < 0.001$) and PLGF ($P = 0.04$). No significant changes in sVEGFR1 ($P = 0.62$), bFGF ($P = 0.13$), or VEGF ($P = 0.35$) were observed. Everolimus compared with placebo was associated with a consistent reduction in the mean fold change from baseline in sVEGFR2 (everolimus vs placebo, respectively: cycle 2, 0.75 vs 0.95; cycle 3, 0.73 vs 0.92; cycle 4, 0.69 vs 0.90; $P < 0.001$ each cycle). This effect was independent of potential prognostic factors, including WHO by histologic grade. Everolimus compared with placebo was associated with a reduction in the mean fold change from baseline in PLGF; however, the overall magnitude of the reduction was small (everolimus vs placebo, respectively: cycle 2, 0.93 vs 1.00 [$P < 0.001$]; cycle 3, 0.98 vs 1.00 [$P = 0.32$]; cycle 4, 1.00 vs 1.01 [$P = 0.34$]).
**Conclusions:** Everolimus demonstrates a significant antiangiogenic effect in patients with advanced pNET. These data confirm previous findings from studies with everolimus in patients with RCC.
Study supported by Novartis.

**6574** POSTER

**Thirty-four Cases of Advanced Ampullary Carcinoma Receiving Non-surgical Treatment − Experience at a Single Center**

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**Background:** Ampullary carcinomas are a fairly disease entity, and little information regarding these tumours, particularly non-surgical treatment, is available. Only one previous report describing 29 patients with advanced ampullary adenocarcinoma treated using cisplatin-based combination chemotherapy has been made (Kim ST et al. Med Oncol.2010). The aim of the present study was to clarify the clinical behavior, treatment strategy, and outcome of ampullary carcinoma treated using a non-surgical approach.
**Methods:** This study retrospectively reviewed data from patients with advanced ampullary carcinoma who receive non-surgical treatment between 1997 and 2010.
**Results:** We identified 34 patients (male/female, 19/15; median age, 62.5 yrs, ranging from 45−79 yrs). Patients characteristics were as follows: adenocarcinoma/neuroendocrine cell carcinoma/undifferentiated carcinoma accounted for 28, 5, and 1, respectively; PS of 0, 1 and 2−4 for 23, 11 and 0, respectively; Stage IV and recurrence accounted for 17 each; and metastatic sites were the liver, lung, lymph nodes, peritoneum and pleura in 22, 7, 21 1 and 1, respectively. The treatment group consisted of chemotherapy (n = 30), TACE (n = 1) and best supportive care (n = 3). The chemotherapy group were treated with 5-FU+CDDP (n = 3), CDDP+Epirubicin+5-FU (n = 1), UFT+Doxorubicin (n = 5), S-1 (n = 3), GEM (n = 11), GEM+CDDP (n = 6) and CDDP+ETP (n = 1). When the data for the adenocarcinoma group who received chemotherapy were analyzed, the over-all response rate was 7.7%. The median progression-free survival was 3.2 months (3.2 months in the 5-FU containing regimen group: 5-FU group vs. 3.8 months in the GEM containing regimen group: GEM group) and the median over-all survival time was 8.2 months (8.0 months in the 5-FU group vs. 9.1 months in the GEM group). There was no statistically significant difference between the 5-FU group and the GEM group.
**Conclusions:** The treatment outcome in patients with advanced ampullary carcinoma was poor. As com-pared with 5-FU-based regimen, the GEM-based regimen showed a favorable outcome, but the difference was not statistically significant.

**6575** POSTER

**Biliary Tract Carcinomas − a Retrospective Analysis of First Line Chemotherapy Based on Platinium Compounds and Second Line Based on 5 Fluororacil**

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**Purpose:** The goal of this study was to examine the survival and safety in patients with metastatic unresecable biliary tract carcinomas (BTC) treated in first line chemotherapy by the association of gemcitabine with

oxaliplatin or carboplatin in our center and to find prognostic factors. We also examined the efficacy of second line chemotherapy based on 5-fluorouracil (5FU).

**Patients and Methods:** Fifty eight patients with metastatic unresecable BTC diagnosed between 2001 and 2010 were studied.

In first line of chemotherapy, a total of 44 patients received gemcitabine 1000 mg/m$^2$ (day 1) and oxaliplatin 100 mg/m$^2$ (day 1), every 2 weeks. 14 patients received gemcitabine at 1000 mg/m(2) on days 1 and 8 with i.v. carboplatin dosed at an area-under-the-curve (AUC) of 5 on day 1 of a 21-day cycle.

In second line a total of 19 patients on 58 received a chemotherapy based on 5FU: 10 a monochemotherapy and 9 a bichemotherapy.

**Results:** With oxaliplatin and gemcitabine there were 3 confirmed complete response (6.8%) (RECIST), 5 partial responses (11.4%), 9 stable disease (20.4%) and 27 progression disease (61.4%). Median overall survival (OS) was 10 months [95% CI,6−17] and progression-free survival (PFS) was 4 months [95% CI,2−10]. The main toxicities were thrombopenia (9.1% grade 2 and 2.3% grade 3) and peripheral neuropathy (20.4% grade 2 and 6.8% grade 3).

With carboplatin and gemcitabine there were 1 complete response (7.1%), 1 partial response (7.1%), 5 stable disease (35.7%) and 7 progression disease (50%). Median overall survival was 4 months [2−10] and progression-free survival was 2 months [0−5]. The main toxicity was haematological: anemia (28.6% grade 2, 50% grade 3, 7.1% grade 4), thrombopenia (28.6% grade 2, 35.7% grade 3, 14.3% grade 4), neutropenia (14.3% grade 2, 35.7% grade 3, 7.1% grade 4).

Age, ECOG, tumour location and number of metastatic sites were not prognostic factors.

In second line the median PFS was 4 months (95% CI, 2−4) for the monochemotherapy group as compared with 3 months (95% CI, 2−4) in the bichemotherapy group. There was no significant difference between the two groups (p = 0.98).

**Conclusion:** The gemox regimen in first line chemotherapy can be considered as a standart arm in the future studies. In second line, monochemotherapy based on 5 fluorouracil seems to be as efficient as bichemotherapy and it should be compared in randomised trials with best supportive cares.

**6576** POSTER

### Phase II Safety Study of the Oral Multikinase Inhibitor Regorafenib (BAY 73–4506) as Second-line Therapy in Patients With Hepatocellular Carcinoma

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**Background:** Regorafenib (BAY 73–4506) is a novel diphenylurea oral multikinase inhibitor of angiogenic (VEGFR1−3, TIE2), stromal (PDGFR-β, FGFR), and oncogenic kinases (KIT, RET, RAF). In preclinical models, regorafenib has shown a broad spectrum of antitumour activity. Regorafenib 160 mg once daily (o.d.) in repeating cycles of 3 weeks on/1 week off was determined as recommended dose for phase II/ III. We report here data from a multicenter, open-label, Phase II safety study of regorafenib in patients with hepatocellular carcinoma (HCC) (ClinicalTrials.gov ID: NCT01003015, sponsored by Bayer).

**Methods:** From September 2009 to November 2010, patients (⩾18 years old) with HCC who had radiological progression on prior first-line sorafenib treatment were enrolled. Other inclusion criteria were Child-Pugh class A, BCLC stage category A, B or C (not benefiting from established therapies), ECOG performance status 0−1, at least one naïve measurable lesion, and adequate bone marrow and organ function. Treatment consisted of regorafenib 160 mg once daily on a 3 weeks on/1 week off schedule. The primary objective of the study was safety evaluation, while the secondary included efficacy parameters, evaluated according to RECIST 1.0 and JNCI amendments in terms of the definition of progressive disease in HCC: time to progression (TTP), objective response rate (ORR), disease control rate (DCR) and overall survival (OS).

**Results:** Thirty-six patients (32 male, 4 female; median age 61 years [range 40−76]) have received ⩾1 dose of regorafenib. Median duration of treatment was 15.5 weeks (range 2–36.0). Common treatment-related adverse events (AEs) (⩾20% of patients, all grades) were hand-foot skin reaction (HFSR) 50%, diarrhea 50%, fatigue 47%, hypothyroidism 36%, anorexia 33%, hypertension 31%, nausea 31%, voice changes 25%, and constipation 22%. Grade 3/4 treatment-related AEs (⩾5% of patients) were HFSR 14% (all grade 3), fatigue 14%, diarrhea 6%, hyperbilirubinemia 6% and hypophosphatemia 6%. All patients were evaluable for efficacy. Stable disease has been observed in 25 patients (69%) and a confirmed partial response in 1 (3%) patient. At the data cut-off, median time to progression was 127 days. Fifteen patients remain on treatment.

**Conclusions:** These data indicate that regorafenib can be administered safely in patients with HCC who have progressed on first-line sorafenib. Preliminary efficacy data indicate promising antitumour activity in this patient population.

**6577** POSTER

### Investigating Potential Biomarkers for Survival With Erlotinib in Patients With Advanced Pancreatic Cancer − Results of the Phase II BO21129 Study

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**Introduction:** Erlotinib is a human epidermal growth factor receptor (EGFR)-targeted agent that in combination with first-line gemcitabine significantly improves progression-free and overall survival (PFS; OS) in pts with advanced pancreatic cancer (Moore et al, 2007). The BO21129 study (sponsor F. Hoffmann-La Roche; ClinicalTrials.gov: NCT00674973) investigated whether patients (pts) with advanced pancreatic cancer likely to benefit from erlotinib therapy can be identified by clinical or molecular biomarkers.

**Methods:** This randomised, placebo-controlled, phase II study enrolled pts with histologically/cytologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer, with ECOG performance status (PS) 0−2 who had failed or were unsuitable for first-line chemotherapy. Pts received placebo or daily oral erlotinib (150 mg) until disease progression with further treatment permitted (including erlotinib for the placebo arm). Primary endpoint was the identification of biomarkers for improved PFS with erlotinib. Other endpoints were OS, response rate, disease control rate (DCR) and adverse events (AEs). Data cut-off was 6 months from last pt randomised; results were stratified by ECOG PS, region and smoking status, and analysed by log-rank test.

**Results:** Baseline characteristics in the overall population (n = 207), and by biomarker status and stratification factor, were similar between arms; the population had a poor prognosis (16% of pts had PS 2) and >50% of pts in the placebo arm received erlotinib on disease progression. PFS in the erlotinib and placebo arms (non-stratified primary analysis) was not significantly different (6.1 weeks and 5.9 weeks, respectively; p = 0.1909). No stratification factor or biomarker (of the 4 initially assessed: EGFR protein expression, *EGFR* gene copy number, *KRAS* mutation and *EGFR* mutation) predicted improved PFS with erlotinib. DCR improved with erlotinib, but this was not statistically significant. OS was not significantly different between the arms. The number of pts with ⩾1 AE (mainly mild/moderate) was higher with erlotinib than placebo (86.5% vs 68.9%, respectively).

**Conclusion:** So far, of those studied, no stratification factor or biomarker predictive of improved PFS with erlotinib has been identified in pts with advanced pancreatic cancer. The safety profile of erlotinib in this poor prognosis population was manageable and similar to prior studies.