to GLU (4500 mg/m^2 IV over 6 hours on Day 1 of every 21-day cycle) or to best supportive care (BSC). Pts were stratified by KPS (80–100 vs 70) and center. The primary endpoint was overall survival. 150 subjects were needed in each arm to detect a 50% improvement in survival (3 vs 4.5 months) with 90% power and 5% Type I error.
Results: 303 pts from 90 global sites were randomized from Sept 04-Aug 06. As of the data cutoff date, 261 pts had died. Two-thirds of subjects were on study for 1 or 2 cycles. An 18% increase in overall survival for GLU was not statistically significant: HR 0.85 (95% CI 0.66−1.08), p = 0.19. Median survival was 105 days for GLU and 84 days for BSC. Median progression-free survival were 46 and 43 days (HR 0.76, 95% CI 0.57−1.02), p = 0.06). Visual analog pain score decreased with time on study for pts on GLU but increased on BSC. There were 3 confirmed responses in the GLU arm and 1 on BSC. Tumor control rates (CR, PR or SD for at least 6 weeks) were 34% for GLU and 24% for BSC. CA19−9 response rates (>50% reduction) were 16% for GLU and 9% for BSC. The most common GLU-related adverse events were nausea (4% Gr 3/4) and vomiting (5% Gr 3/4). Serious adverse events (SAE) occurred in 16.3% on GLU and 10.3% on BSC. Eleven pts died due to SAE: 5 on GLU and 6 on BSC. Grade 3/4 neutropenia and thrombocytopenia were uncommon (4.8 and 3.2%) on GLU. Grade 3/4 creatinine increase occurred in 6 pts on GLU, including 3 with dosing errors. CrCL fell to <60 mL/min in 25% on GLU and 12% on BSC.
Conclusions: These results suggest modest activity of GLU in this very refractory patient population. Nephrotoxicity was similar to that observed in the Phase I and II trials.

3506 ORAL

Axitinib (AG-013736) and gemcitabine vs gemcitabine in advanced pancreatic cancer: a randomised phase II study

J. Spano[1], C. Chodkiewicz[2], J. Maurel[3], R. Wong[4], H.S. Wasan[5], C. Barone[6], K.F. Liau[7], Y. Pithavala[7], P.W. Bycott[7], O. Rixe[1].
[1]GH Pitié-Salpétrière, Département d'Oncologie Médicale, Paris, France; [2]Moffitt Cancer Center, Gastrointestinal Tumor Experimental Therapeutics, Tampa, USA; [3]Hospital Clinic de Barcelona, Medical Oncology, Barcelona, Spain; [4]Cancer Care Manitoba, Medical Oncology, Winnipeg, Canada; [5]Hamersmith Hospital, Medical Oncology, London, United Kingdom; [6]Universita Cattolica del S. Cuore, Medical Oncology, Rome, Italy; [7]Pfizer Inc., Global Research & Development, La Holla, USA

Background: Gemcitabine-based chemotherapy is the current standard of care for patients (pts) with advanced pancreatic cancer (APC). Axitinib is a potent inhibitor of vascular endothelial growth factor receptors (VEGFR). A phase 1 study of axitinib in solid tumours identified 5 mg BID as the therapeutic starting dose. The lead-in phase 1 component of the current study indicated that gemcitabine doses of 1000 mg/m^2 administered over 30 minutes on days 1, 8 and 15 every 28 days in combination with axitinib 5 mg po BID was well tolerated. The pharmacokinetics of gemcitabine and axitinib appeared to be unchanged when combined. In this randomised phase 2 trial of first-line therapy for pts with APC, we aim to determine whether the overall survival (OS) of pts receiving combination therapy with axitinib and gemcitabine is superior to that of pts receiving gemcitabine alone.
Methods: In the randomised phase 2 component of the trial, 103 pts with locally advanced or metastatic disease, no prior gemcitabine or VEGF/VEGFR inhibitors, ECOG PS 0–2 were randomised (2:1) to gemcitabine 1000 mg/m^2 over 30 minutes on days 1, 8 and 15 every 28 days with (Arm A) or without axitinib (Arm B) at a starting dose of 5 mg po BID between January 06 and August 06. CT scans were performed every 2 cycles.
Results: The demographics were well balanced in the two arms (Arms A:B): males (51%:48%), mean age (63.6:60.2), ECOG PS 0/1 (91%:91%), and locally advanced disease (40%:38%). Grade $\geqslant$3 haematological AEs were anaemia (14%:22%), leucopenia (18%:15%), neutropenia (28%:30%), thrombocytopenia (17%:15%), and lymphopenia (14%:22%). The most common non-haematological AEs were fatigue (45%:32%), diarrhoea (41%:26%), nausea (37%:42%), vomiting (33%:39%), anorexia (28%:19%), asthenia (27%:13%), hypertension (20%:3%), constipation (20%:23%), dyspnea (20%:13%), pyrexia (16%:26%), dysphonia (16%:0%), mucositis (15%:3%), stomatitis (15%:7%), abdominal pain (13%:26%), decreased weight (13%:13%), pruritus (13%:3%), alopecia (11%:0%), dizziness (11%:10%), decreased performance status (11%:0%) and pain (11%:7%). An interim analysis performed at 55 events showed a pooled median OS of 204 days (95% CI: 159, not estimable). The median follow-up time is currently 224 days.
Conclusions: Axitinib can be administered safely at a starting dose of 5 mg BID in combination with standard-dose gemcitabine in pts with APC. Final OS results by treatment arm will be presented.

3507 ORAL

Sorafenib improves survival in a large multi-center, randomized, placebo-controlled phase III trial in patients with hepatocellular carcinoma

J. Llovet[1,2], V. Mazzaferro[3], S. Ricci[4], P. Hilgard[5], J. Raoul[6], S. Zeuzem[7], M. Shan[8], M. Moscovici[9], D. Voliotis[10], for the SHARP investigators Study Group. *[1]University of Barcelona, IDIBAPSLiver Unit, Barcelona, Spain; [2]University of Barcelona, BCLC Group Liver Unit, Barcelona, Spain; [3]National Cancer Institute, Gastrointestinal surgery/liver transplant unit, Milan, Italy; [4]St Chiara University Hospital, Department of medical oncology, Pisa, Italy; [5]University Hospital Essen, Department of gestroenterology and hepatology, Essen, Germany; [6]Centre Eugene Marquis, Department of medical oncology, Rennes, France; [7]JW Goethe University Hospital, Department of medical oncology, Frankfurt, Germany; [8]Bayer Healthcare pharmaceuticals, medical oncology, West Haven, USA; [9]Bayer Shering Pharma, medical oncology, Milan, Italy; [10]Bayer Shering Pharma, Global Clinical development, Wuppertal, Germany*

Background: Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide. HCC is very difficult to treat and carries a poor prognosis. No systemic chemotherapy regimens are effective in advanced HCC and thus, effective treatment options are urgently needed. Sorafenib, a kinase inhibitor with multiple targets, including Raf and VEGFR, has demonstrated activity in advanced HCC in a phase II trial. Here we report the findings of a large, multicenter, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with HCC.
Methods: Patients with advanced measurable HCC, no prior systemic treatment, ECOG PS 0−2 and Child-Pugh status A received sorafenib (Sor) 400 mg bid or placebo (P). Primary efficacy endpoints were overall survival (OS) and time to symptomatic progression (TTSP). Time to progression (TTP) and disease control rate (DCR; CR+PR+SD for at least 2 cycles) were secondary endpoints.Treatment arms were compared for OS and TTSP using a 1-sided log-rank test [overall α of 0.02 (OS) and 0.005 (TTSP)] stratified by region, ECOG PS and tumor burden. An O'Brien-Fleming-type error spending function determined criteria for early stopping for efficacy.
Results: 602 patients (Sor n = 299; P n = 303) were randomized. Baseline characteristics were similar for Sor vs P: median age (67 vs 68 y), male (87% vs 87%), ECOG PS 0 (54% vs 54%), Child-Pugh A (95% vs 98%), and BCLC stage C (82% vs 83%). Based on 321 deaths (Sor n = 143; P n = 178), the hazard ratio (HR) for OS (Sor/P) was 0.69 (95% CI: 0.55, 0.87; p = 0.0006), representing a 44% improvement in OS vs P which met early stopping criteria. Median OS was 10.7 vs 7.9 mos (Sor vs P). Primary TTSP analysis demonstrated no statistically significant difference for Sor versus P. HR for TTP (independent assessment) was 0.58 (95% CI: 0.45, 0.74; p = 0.000007). Median TTP was longer (5.5 vs 2.8 mos) and DCR was higher (43% vs 32%) with Sor versus P. Incidence of serious adverse events was similar for Sor verus P (52% vs 54%). The most frequent grade 3/4 events were diarrhea (11% vs 2%), hand–foot skin reaction (8% vs 1%), fatigue (10% vs 15%), and bleeding (6% vs 9%) for Sor versus P.
Conclusions: Sorafenib was well tolerated and is the first agent to demonstrate a statistically significant improvement in OS for patients with advanced HCC. This effect is clinically meaningful and establishes sorafenib as first-line treatment for these patients.

Poster presentations (Wed, 26 Sep, 09:00−12:00)
Gastrointestinal cancer – non colorectal

3508 POSTER

Hugl-1 mutation has a correlation with the hepatocellular carcinoma progression

X. Lu. *Institute of Biochemistry and Cell Biology, cell biology, Shanghai, China*

Background: The tumor suppressor lethal giant larvae (Lgl) plays a critical role in epithelial cell polarization in Drosophila. Loss of Lgl function leads to failure of cell polarization, uncontrolled proliferation and growth of neoplastic lesions. Although down-regulation of the human lgl homologous, Hugl-1, was found to be correlated with metastasis of human cancers, whether it functions as a tumour suppressor was not clear, as no mutation in Hugl-1 gene has been reported so far.
Materials and Methods: Mutation and aberrant splicing of Hugl-1 were characterized by reverse-transcription polymerase chain reaction (PCR) and direct-sequencing of PCR products. The expression levels of Hugl-1 mRNA and protein were analysed by real-time PCR, Northern blot, in situ hybridization and Western blot. Biological activities of Hugl-1 and

its aberrant spliced variants in the hepatocellular carcinoma cells were evaluated through MTT assay, wound healing assay and Boyden Chamber assay.
Results: Twenty aberrant splicing forms of Hugl-1 mRNA were identified in 20% (1/5) hepatocellular carcinoma cell lines and 30.77% (24/78) hepatocellular carcinoma specimens, but not their adjacent noncancerous tissues. Sequence analysis of all aberrant spliced forms of Hugl-1 revealed that a striking feature common to 95% of the aberrant forms is that small direct-repeat sequences (3−10 bp) flank the deleted regions of Hugl-1. In addition, somatic mutation in Hugl-1 was also found in 7.5% (6/78) hepatocellular carcinoma specimens. Statistic analysis shown that the abnormal splicing of Hugl-1 was significantly correlated with poor differentiation of hepatocellular carcinoma ($P = 0.011 < 0.05$) and large tumor size ($P = 0.019 < 0.05$). Interestingly, we also found that 75.9% (41/54) of hepatocellular carcinoma tissues displayed high, even over-expression of Hugl-1 compared to their adjacent noncancerous tissues. Overexpression of Hugl-1/wt inhibited migration and invasion of Sk-Hep1 cells. In contrast, expression of two abnormal spliced forms of Hugl-1 significantly promoted the both actions of the tumor cells.
Conclusions: Our data imply that the aberrant splicing and mutation of Hugl-1 may play an important role in development of hepatocellular carcinoma.

3509 POSTER

Growth inhibitory effects and mechanisms of lapatinib, a dual inhibitor of ErbB1 and ErbB2 tyrosine kinase, in gastric cell lines

J.W. Kim[1], S.A. Im[2], H.P. Kim[3], D.Y. Oh[2], T.Y. Kim[2], Y.J. Bang[2]. *[1]Seoul National University, Internal Medicine, Seoul, Korea; [2]Seoul National University, Internal Medicine & Cancer Research Institute, Seoul, Korea; [3]Seoul National University, Cancer Research Institute, Seoul, Korea*

Background: Lapatinib (GW572016) is a dual inhibitor of both ErbB1 (epidermal growth factor receptor: EGFR) and ErbB2 tyrosine kinases. HER-2 gene amplification and protein overexpression occur in 10−20% of gastric cancer. We explore the therapeutic potential of lapatinib by testing its effect on gastric cancer cell lines.
Materials and Methods: We tested the in vitro growth inhibitory effect of lapatinib and molecular mechanism in gastric cancer cell lines (SNU-1, 5, 16, 216, 484, 601, 620, 638, 668, 719, NCI-N87) and ErbB2 amplified breast cancer cell SKBR3 as positive control. ErbB1 and ErbB2 amplification were identified through fluorescence in-situ hybridization (FISH). Growth inhibitory effect was assessed by tetrazolium bromide (MTT) assay. In relatively sensitive cell lines, cell cycle analysis at various conditions of lapatinib was done using flow cytometry and down-stream molecules were analyzed using immunoprecipitation and Western blot analysis. Interaction of lapatinib with cytotoxic agents (5-FU, cisplatin, oxaliplatin, paclitaxel) was evaluated by combination index.
Results: ErbB2 amplification were detected in SNU-216 and NCI-N87 gastric cancer cell lines. These two gastric cancer cell lines were sensitive to lapatinib as much as SKBR3 (IC50 = 0.02, 0.01, 0.018 respectively). None of gastric cancer cell lines showed ErbB1-amplification. Lapatinib induced G1 arrest as dose- and time-dependent manners in SNU-216 and NCI-N87. In NCI-N87, apoptosis was induced dominantly. In lapatinib-treated SNU-216 and NCI-N87, phosphorylation of ErbB1 and ErbB2 was inhibited. And then, phosphorylation of Akt and Erk was down-regulated. In NCI-N87, apoptotic molecules of PARP and casepase-3 were induced. Lapatinib treatment with 5-FU, cisplatin, oxaliplatin or paclitaxel resulted in additive or synergistic inhibitory effect. Lapatinib induced downregulation of thymidylate synthase, which is a target enzyme of 5-FU.
Conclusions: Lapatinib showed the growth inhibitory effect in the ErbB2-amplified gastric cancer cell lines as single agent and with combination of clinically relevant cytotoxic agents. This opens up the possibility of considering lapatinib as a therapeutic agent in gastric cancer.

3510 POSTER

Serum vascular endothelial growth factor (VEGF), VEGF receptor-1 and -2 among gastric cancer patients and healthy subjects

S. Kikuchi[1], Y. Obata[2], K. Yagyu[1], Y. Lin[1], T. Nakajima[3], O. Kobayashi[4], M. Kikuichi[5], K. Ohta[6], R. Ushijima[7]. *[1]Aichi Medical University School of Medicine, Public Health, Aichi, Japan; [2]Kinjogakuin University, Pharmacy, Aichi, Japan; [3]Cancer Institute Hospital, Surgery, Tokyo, Japan; [4]Kanagawa Cancer Center, Surgery, Kanagawa, Japan; [5]Mitsui Memorial Hospital, Surgery, Tokyo, Japan; [6]International University of Health and Welfare Mita Hospital, Surgery, Tokyo, Japan; [7]Suifu Hospital, Surgery, Ibaraki, Japan*

Background: Vascular endothelial growth factor (VEGF) is a factor promoting vascularization including that of malignant tumors and serum VEGF concentration is high in patients with several cancers. Its receptor proteins-1 (VEGFR-1) and -2 (VEGFR-2) are also detected in serum. To date, VEGF is known to be higher among gastric cancer patients than among healthy subjects, but there is not sufficient data on VEGFR-1 or VEGFR-2.
Subjects and Methods: Subjects are 164 primary gastric cancer patients aged 23 to 69 years and 164 apparently healthy subjects (controls) paired one to one with the patients (matched for age [within 2 years] and gender). Using sera from the subjects, VEGF, VEGFR-1 and VEGFR-2 were measured and compared between the patients and controls. Comparison by paired t test was performed using all pairs and restriction pairs to ones with early (depth was within submucosa), advanced (deeper), intestinal or diffuse type cancer.
Results: Among the controls and patients, VEGF (pg/ml) was 479 ± 351 (mean $\pm$ standard deviation) and 641 ± 517 (164 pairs, $p = 0.001$), VEGFR-1 (pg/ml) was 56.0 ± 34.3 and 48.5 ± 32.5 (147 pairs, $p = 0.066$), and VEGFR-2 (pg/ml) was 8850 ± 1890 and 8400 ± 2010 (164 pairs, $p = 0.022$), respectively. Significant or nearly significant differences between patients and controls were observed among early cancer pairs of VEGF (78 pairs, $p = 0.057$), among advanced cancer pairs of VEGF (86, $p = 0.009$) and VEGFR-2 (86, $p = 0.003$), among intestinal type cancer pairs of VEGF (63, $p = 0.026$), and among diffuse type pairs of VEGF (101, $p = 0.018$), VEGFR-1 (90, $p = 0.064$), VEGFR-2 (101, $p = 0.002$).
Conclusion: VEGF was higher and VEGFR-1 and VEGFR-2 were lower among gastric cancer patients than among controls. Compared with early cancer, advanced cancer showed clearer difference with controls. Diffuse type cancer patients gave clearer difference of VEGFR-1 and VEGFR-2 with controls than intestinal type did, while such effect of pathological was not observed on VEGF.

3511 POSTER

Improved in vitro and in vivo efficacy in pancreatic cancer therapy in SCID mice by a new endostatin–albumin fusion protein

C. Dietz[1], O. Kisker[1], O. Sürücü[2], P. Mertins[3], E. Karakas[4], M. Rothmund[4], I. Celik[5]. *[1]Philipps University, Visceral-thoracic and vascular surgery, Marburg, Germany; [2]Philipps University, Institute of Theoretical Surgery, Marburg, Germany; [3]ZLB Behring GmbH, P.O. Box 1230, Marburg, Germany; [4]Philipps Universitiy, Visceral-thoracic and vascular surgery, Marburg, Germany; [5]Philipps Universitiy, Institute of Theoretical surgery, Marburg, Germany*

Background: Endostatin is a potent endogenous inhibitor of angiogenesis. Additionally it could be shown that continuous application via intraperitoneally implanted pumps in mice is superior to bolus injections of endostatin. Aim of the study was to investigate the antiangiogenic and antitumor effects in vitro and in vivo of a new albumin endostatin fusion protein (AFP-endostatin) with increased half-life in a pancreatic cancer model.
Materials and Methods:
1. In a first step recombinant human AFP-endostatin was generated and expressed in yeast.
2. In the second step pharmacokinetic studies of AFP-endostatin versus rh-endostatin (Calbiochem) applicated intravenously (i.v.) and subcutaneously (s.c.) were performed to survey Cmax, half-life and optimal dosage. The measurement of endostatin serum levels were performed by ELISA (Cytimmune). Additionally HUVEC migration assays were conducted with AFP-endostatin and rh-endostatin (Calbiochem) 0.03−40 μg/ml.
3. Finally the in vivo efficacy was investigated. In male immuno-deficient mice (SCID, 6−8 weeks old) BxPC-3 pancreatic cancer cells (2.5×10^6 in 0.2 ml RPMI 1640 medium) were implanted s.c. in the midline dorsa of the mice (n = 7/group). Tumour volume was measured every 3−5 days with the digital calliper. Mice were randomised in therapy and control groups when tumour size reached 100 ± 20 mm3. Animals in the 4 therapy groups were treated by s.c. AFP-endostatin application: 0.5 mg/kg/24h; 0.4 mg/kg/72h; 1.2 mg/kg/72h; 3.6 mg/kg/72h versus daily PBS (placebo) application (n = 7/Gruppe) for 23 days. The applications were performed s.c. in an adequate distance from the tumor. Tumor volume was measured every 3−5 days with the digital calliper.

Results:
1. AFP-endostatin could be successfully generated and expressed in yeast.
2. The half-life for AFP-endostatin (56h) versus rh-endostatin (4.5h) was significantly increased. Migration assay showed 66% inhibition (0.2 μg/ml) for AFP-endostatin versus 87% inhibition (rh-endostatin).
3. Similar tumour inhibition rate could be shown for 0.5 mg/kg/24h (84% Inhibition) and 1.2 mg/kg/72h (78% Inhibition). A clear dose-response for the 72 h application schedule could be demonstrated. For 0.4 mg/kg/72h; 1.2 mg/kg/72h and 3.6 mg/kg/72h AFP-endostatin an inhibition rate of 61%; 78% and 92% respectively could be observed. No side effects or weight loss was observed during the whole experiment.