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