Methods: Patients (pts) were randomized to receive FLO: F 2600 mg/m^2 24h infusion, L 200 mg/m^2, and oxaliplatin 85 mg/m^2, every two weeks or FLP: F 2000 mg/m^2 24h infusion, L 200 mg/m^2, weekly, and cisplatin 50 mg/m^2, every two weeks. The primary end point was PFS (power, 80%; 1-sided log-rank test; significance level 0.05).
Results: 220 pts were randomized (FLO, 112; FLP, 108) between Aug 2003 and Jan 2006. Median age was 64 years and median ECOG was 1. Median treatment duration was 4.3 months with FLO and 3 months with FLP. FLO was associated with significantly less NCI-CTC grade 1−4 anemia (54% v 82%), nausea (57% v 71%), vomiting (37% v 52%), alopecia (22% v 39%), fatigue (20% v 36%), renal toxicity (11% v 34%), and serious adverse events related to the treatment (9% v 19%), and FLP was associated with significantly less peripheral neuropathy (25% v 60%). There was a trend toward increased median PFS with FLO versus FLP (5.7 months v 3.8 months, respectively), which did not reach the statistical significance (P=.0725). OS was 10.8 months for FLO and 8.7 months for FLP (NS). However, in pts aged >65 years (n = 94), treatment with FLO resulted in a significantly superior response rate (34.9% v 16.7%), time to treatment failure (5.4 v 2.1 months, p = 0.0001), and PFS (6.0 v 3.1 months, p = 0.021). These differences seemed also to result in an improved OS in elderly pts treated with FLO (13.8 v 7.3 months, p = 0.081). In contrast, there were no significant differences in young pts between arms concerning all efficacy parameter.
Conclusions: FLO reduced toxicity and, in elderly pts, improved efficacy as compared to FLP. This leads us to consider FLO for future studies in combination with targeted drugs to further improve the outcome of pts with gastric cancer.

3503 ORAL

Adding external beam to HDR-intraluminal brachytherapy, improves palliation of oesophageal cancer: a prospective randomized, multicentre trial of the International Atomic Energy Agency

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Background: While the addition of oesophageal high dose-rate intraluminal brachytherapy (HDR-ILBT) has shown improved palliation compared with external beam radiation therapy (EBRT) alone, it is not known whether the addition of EBRT adds to the benefits of ILBT alone. This study aims at identifying resource-sparing treatment strategies to be adopted in low-income developing countries.
Methods: Patients were recruited in 6 countries where oesophageal cancer is common. Patients had localized non-metastatic, squamous-cell carcinoma, not amenable to curative therapy. They were managed with two ILBT of 8 Gy each, at 1 cm of the sources centres, and were randomized to EBRT of 30 Gy in 10 fractions vs. no EBRT. Worsening of dysphagia and the occurrence of a fistula were combined into a "dysphagia-free experience" (DFE) plot. Study endpoints were DFE, dysphagia score, ECOG performance status, quality of life and weight. Patient survival was not an endpoint in this study.
Results: 219 patients were randomized: 110 received EBRT and 109 did not. Patient characteristics, disease stage, symptoms and quality of life in both groups were similar. The main outcome of DFE was significantly improved with EBRT, by an absolute 18% (a sustained difference from 50 to 350 days of follow-up from randomization), with p = 0.019 by log-rank. Mean dysphagia scores were 0.79 with combined therapy and 1.23 with brachytherapy alone, a difference of 0.44 in favour of EBRT. Mean regurgitation scores were 0.36 and 0.72, respectively, a difference in favour of combined therapy. Adverse events were not different between the two study groups (e.g. perforations, ulcers). In particular, occurrences of strictures were in 5 cases with EBRT, and 1 without EBRT (p = 0.21), while occurrences of fistulae were in 12 cases with EBRT, and 7 without EBRT (p = 0.34); and the combined risks of either stricture or fistula at one-year were approximately 25% in both study groups. Overall median survival was 188 days; with no difference between study arms (p = 0.35). Performance status (an ECOG score difference of −0.40), and some quality of life measures ("activity level" and "feeling of well-being") were significantly improved with EBRT. Hierarchical multivariate analyses confirmed the findings regarding the benefits of combined therapy relative to brachytherapy alone.
Conclusions: The addition of EBRT to HDR-ILBT improves palliation in patients with squamous cell carcinoma of the oesophagus.

3504 ORAL

A randomized phase III study comparing gemcitabine monotherapy with observation in patients with resected pancreatic cancer

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Background: Gemcitabine (Gem) is considered to be a standard chemotherapy for unresectable advanced pancreatic cancer. However, the role of Gem in patients (pts) with resectable pancreatic cancer is uncertain. This study was designed to determine whether adjuvant chemotherapy with Gem improves the outcome of pts with resected pancreatic cancer.
Materials and Methods: This randomized phase III study was conducted at 10 centers in Japan. Eligibility criteria included gross complete resection of invasive ductal carcinoma of the pancreas and no prior radiation or chemotherapy. Pts were randomized to receive Gem monotherapy or observation using the minimization method stratified by pathological stage (UICC 5th edition stage I, II vs. III, IV), resection status (R0 vs. R1) and centers. Gem was administered at a dose of 1,000 mg/m^2 over 30 min on days 1, 8, and 15 every 4 weeks for 3 cycles. The primary end point was overall survival (OS), and secondary end points were disease-free survival (DFS) and adverse events.
Results: Between April 2002 and March 2005, 119 pts were entered into the study. Among them, 118 pts were eligible and analyzable (58 in the Gem arm, 60 in the observation arm). Both arms were well balanced in terms of baseline characteristics. Although hematologic toxicity was frequently observed in the Gem arm (grade 3 or 4 leukopenia 24.6%, grade 3 or 4 neutropenia 70.2%), most toxicities were transient, and grade 3 or 4 non-hematologic toxicity rarely occurred. During a mean follow-up period of 21.2 months, 42 pts (72.4%) in the Gem arm and 51 (85.0%) in the observation arm developed recurrent disease. Pts in the Gem arm demonstrated significantly longer DFS than those in the observation arm (median DFS, 11.44 months vs. 4.97 months; hazard ratio = 0.59 [95% confidence interval: 0.39−0.89]; P = 0.01). Also, the median OS of pts in the Gem arm was better than that of pts in the observation arm (median OS, 22.31 months vs. 18.36 months), although not to a significant degree (hazard ratio = 0.79 [95% confidence interval: 0.51−1.22]; P = 0.29).
Conclusions: Adjuvant chemotherapy with Gem significantly improved DFS compared with observation in pts with resected pancreatic cancer. OS was also more favorable in the Gem arm, although the difference did not attain statistical significance. We conclude that adjuvant chemotherapy with Gem may be considered as an optimal treatment in pts scheduled for resection of pancreatic cancer.

3505 ORAL

Glufosfamide (GLU) in metastatic pancreatic adenocarcinoma previously treated with gemcitabine: Results of a Phase III trial

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Background: Glufosfamide is glucose linked to isophosphoramide mustard, the active metabolite of ifosfamide. Cancer cells use glucose at a higher rate than normal cells, which may lead to preferential metabolic targeting by GLU.
Methods: Patients (pts) with metastatic pancreatic adenocarcinoma previously treated with gemcitabine and with adequate KPS and renal (CrCL $\geqslant$ 60 mL/min), hepatic and hematologic function were randomized

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

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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

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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

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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