preoperative CRT [CRT-S] group and 41 in the surgery alone [S] group) were available for immunohistochemical analysis. ERCC1 expression were classified into positive (score >4) and negative (score⩽4) based on median value of ERCC1 expression. Patients and disease characteristics were comparable between 2 groups. ERCC1 expression was positive in 71 patients (47%). With a median follow-up of 44 months, median overall survival (OS) of surviving patients was 45.6 months in the S group and 47.8 months in the CRT-S group, and median event free survival (EFS) was 36.7 months in the S group and 38.4 months in the CRT-S group. Neither EFS nor OS differed between groups (p = 0.763 and 0.462, respectively). However, among patients with ERCC1-negative tumors, those who received preoperative CRT had longer OS and EFS compared with those treated with esophagectomy alone (median OS; 59.2 months vs 29.4 months, p = 0.0568, median EFS; 50.7 months vs 19.7 months, p = 0.0415) but not among patients with ERCC1-positive tumors (p = 0.304 and 0.516, respectively). Among patients who received esophagectomy alone, those with ERCC1-positive tumors had a tendency toward longer OS and EFS compared to those with ERCC1-negative tumors (p = 0.085 and 0.094, respectively).
**Conclusions:** Patients with ERCC1-negative tumors may benefit from preoperative CRT compared with surgery alone in resectable esophageal cancer.

**3535** POSTER

**Phase II trial investigating the efficacy and safety of sunitinib in patients with unresectable hepatocellular carcinoma (HCC)**

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**Background:** The oral multitargeted tyrosine kinase inhibitor, sunitinib malate (SUTENT®; SU), has demonstrable antitumour activity and is approved for the treatment of advanced RCC and imatinib-resistant or intolerant GIST. The tyrosine kinases VEGFR and PDGFR, which play key roles in HCC proliferation and tumour angiogenesis, are targets for SU. In this phase II, open-label, single-agent study, we investigate the efficacy and safety of SU in European/Asian patients (pts) with unresectable HCC.
**Patients and Methods:** Pt eligibility criteria included histologically confirmed HCC, ECOG PS ⩽ 1, CP score −A/−B, adequate organ function and no brain metastases, clinically relevant ascites or prior liver transplant. Pts received SU 50 mg/day for 4 wks, every 6 wks (4/2 schedule). The primary endpoint was ORR measured by RECIST. Other endpoints included time-to-event rates, safety (NCI CTCAE v3.0), PK and other measures of antitumour activity (tumour density, volumetric measurement of percent tumour necrosis [VMTN] and intra-tumour blood perfusion by CT scan).
**Results:** Baseline pt characteristics were: n = 37; median age=61 yrs, range 29–82; male=92%; PS 0:1, 51%:49%; CP −A/-B, 84%/16%; 40.5% with prior local treatments. Pts received a median of 2 SU cycles (range 1–8). RECIST assessment indicated one partial response and 35% with stable disease. Median overall survival was estimated to be 45 wks (range 22.0–not reached). Grade 1/2 skin toxicity was common. Grade 3/4 toxicities included thrombocytopenia (35%), neutropenia (24%), CNS symptoms (22%), asthenia (22%) and haemorrhage (22%). Grade 5 events included bleeding, drowsiness, hepatic encephalopathy and renal failure (n = 4). 43% of pts required at least one SU dose reduction. There were no differences in drug exposure between CP-A and −B groups. Tumour density decreased in 68% of pts. Major (>50%) and minor (<50%) post-treatment tumour necrosis, measured by VMTN, occurred in 46% and 25% of pts, respectively. A 39% decrease (range 13–72%) in post-treatment tumour blood perfusion parameters (blood volume and flow) occurred.
**Conclusions:** Major tumour necrosis was observed in almost half of pts in this study following SU treatment, suggesting potent antitumour activity of SU in unresectable HCC. Change in tumour size may not be the most appropriate endpoint for assessing SU efficacy in HCC pts. These findings, which are consistent across European and Asian pts, warrant further investigation of SU in this pt population.

**3536** POSTER

**A phase II study of induction chemotherapy with gemcitabine plus S-1 (GS) followed by chemoradiation for locally advanced pancreatic cancer (LAPC)**

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**Background:** Most patients (pts) with LAPC treated by chemoradiation (CRT) eventually develop metastasis progression. Thus, effective systemic chemotherapy is required, even for pts with LAPC. Gemcitabine plus S-1 (GS) chemotherapy has been shown to yield a high tumor response rate in cases of advanced pancreatic cancer. Here, we conducted an early phase II study to examine the efficacy of GS therapy followed by CRT in pts with LAPC.
**Methods:** The eligibility criteria for enrolment in the trial were: histologically proven LAPC, age >20 years, performance status (PS) of 0 or 1, and no history of prior therapy. The pts received 4 cycles of induction GS chemotherapy (gemcitabine, 1000 mg/m$^2$, days 1, 8; S-1, 40 mg/m$^2$ bid, days 1−14; every 21 days). Subsequently, pts who did not show progression received CRT (30 Gy, 10 fractions, 2 weeks; gemcitabine, 250 mg/m$^2$, days 1, 8). After the CRT, at least 2 cycles of standard gemcitabine (1000 mg/m$^2$, days 1, 8, 15; every 28 days) were administered. The primary endpoint of the study was the progression-free survival (PFS) rate at 6 months. A PFS of 50% at 6 months was expected in this trial.
**Results:** Between February 2005 and October 2006, 20 pts (median age: 63.5 years [33−75 years], PS 0/1: 15/5, male/female: 10/10) were enrolled. The induction GS chemotherapy was completed in 18 pts. Two pts showed disease progression (general deterioration) during the induction GS chemotherapy. Grade 3/4 hematological toxicities were observed in 13 pts (65%), and grade 3 febrile neutropenia was observed in 1 patient. Grade 3 non-hematological toxicities were observed in 5 pts (nausea and anorexia were the most common). Dose reduction was necessitated in 5 pts (25%). Two pts showed disease progression after completion of the induction GS chemotherapy. Subsequently, 16 pts received CRT, which was completed without delay in all. Grade 3 hematological toxicities were observed in 2 of these 16 pts. Five (25%) partial response were observed among all evaluable pts. Laparotomy with curative intent was undertaken in 4 pts, and R0 resection could be accomplished in 3. A pathological complete response was observed in 1 of these patients. The PFS rate at 6 months was 70% (14/20, 95% CI: 45.7−88.1%). The median overall survival period was 11.0 months (95% CI: 5.4−16.5 months).
**Conclusions:** Induction GS chemotherapy followed by CRT is a feasible and promising strategy for the treatment of LAPC. A multicenter trial on a larger sample size is warranted to confirm the efficacy and survival benefit of this treatment observed in this study in patients with LAPC.

**3537** POSTER

**Variations in KIT and PDGFRA mutations in gastrointestinal stromal tumours**

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Gastrointestinal stromal tumors (GISTs) are characterized with oncogenic mutations, leading to constitutive, ligand independent activation of KIT tyrosine kinase. KIT (CD117) appeared to be an extremely helpful marker in discriminating GISTs from other mesenchymal tumors. In GISTs with wild-type KIT protein the mutations in PDGFRA gene were shown. To determine the KIT and PDGRFA mutations in GISTs and estimate their prognostic value, we analyzed 68 genomic DNA extracted from paraffin sections. DNA was amplified with primers to exons 11, 9, 13, 17 of KIT and exon 18 of PDGRFA followed with direct sequencing. Seventy three percents of GISTs harbor KIT mutations in exon 11, namely, 74% of gastric tumors, 63% of intestinal tumors and 100% of GISTs of rectum. The most frequent mutations were in-frame deletions in the region of 550–563aa at the 5′-end of KIT exon 11. The point mutations were localized in 557, 559 and 560 codons. GISTs with KIT mutations that targeted to 557, 558

or 559aa in the 5′-end of exon 11 were low differentiated tumors with recurrences or metastases. There was one gastric GIST with the deletion of 550–558aa that started in KIT intron 10 and involved the intron 10 – exon 11 boundary. There were rather frequent mutations in the 3′-end of KIT exon 11: 20% of GISTs demonstrated in-frame deletions or duplications of 1−12 aminoacid residues in the region of 569–586aa of KIT. Insertions in the 3′-end of KIT exon 11 were found predominantly in GISTs of low malignancy in women over age 65. KIT mutations in exon 9 (duplications of 502–503aa) were detected in 26% of intestinal GISTs. There was one gastric GIST with mutation in KIT exon 17. PDGRFA mutations in exon 18 were found in 8% of GISTs. Substitution D842V was found only in one benign gastric GIST with epithelioid cell morphology. The other PDGRFA mutations were size-altering deletions, involving 842–846aa. There were five GISTs with wild-type KIT and PDGFRA. The obtained results revealed some correlations between the type of KIT and PDGRFA mutations and clinicopathologic parameters of GISTs. They support the suggestion that mutation analysis may be used as additional parameter for predicting GISTs prognosis and response to target-affective therapy.

**3538** POSTER

**Phase I study of concurrent chemoradiation including twice-weekly low dose gemcitabine for unresectable pancreatic adenocarcinoma**

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**Background:** To determine the maximum tolerated dose (MTD) and dose-limiting toxicities, as well as potential antitumor activity of twice-weekly gemcitabine and concurrent irradiation in patients presenting with unresectable locally advanced, or metastatic and painful pancreatic adenocarcinoma.
**Materials and Methods:** Thirty six patients with histologically proven adenocarcinoma of the pancreas have been treated in Centre Hospitalier Lyon Sud, France, between 2000 and 2005. The initial dose of gemcitabine was 30 mg/m$^2$ by 30-minute intravenous infusion twice a week, for 5 consecutive weeks concurrent with 50 Gy of radiation within 5 weeks, delivered to the pancreatic area. Gemcitabine doses were escalated in 10 mg/m$^2$ increments in successive cohorts of three to six patients until dose-limiting toxicities were observed. A limiting toxicity is defined as a grade 4 or 5 toxicity.
**Results:** Thirty six patients have been included, mean age 57 years old (38−73), 25 male and 11 female, all evaluable. Concurrent radiation and twice-weekly gemcitabine at 30-, 40-, 50-, 60-, 70 mg/m$^2$ were well tolerated, without limiting toxicities observed. All patients received the full dose of radiation, and 16/24 (67%) patients received at least 70% of the prescribed dose. At level 80 mg/m$^2$ twice a week, 2/6 limiting toxicities have been observed: radiation-induced Gr. 4 gastric ulcer with vomiting and radiation-induced Gr.4 eso-gastritis. At this level, all patients received the full dose of radiation, and the mean gemcitabine delivered dose was 616 mg/m$^2$, i.e. 77% of the prescribed dose. The MTD for twice-weekly gemcitabine is 80 mg/m$^2$, the recommended dose 70 mg/m$^2$.
**Conclusions:** Definitive results will be presented for the first time, with a recommended dose 70 mg/m$^2$ when twice-weekly Gemcitabine and radiation are delivered. The complete cohort of patients will be finally analyzed for toxicity, survival and relapse patterns. The next phase I trial will include new agents in addition to gemcitabine and radiation, for the same type of patients.

**3539** POSTER

**High-dose 3D-Conformal Radiation Therapy (CRT): a new curative treatment for patients with small hepatocellular carcinomas (HCC). Mature results of a French phase II trial (RTF1)**

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The aim of this phase 2 trial was to evaluate the tolerance and efficacy of high-dose conformal radiotherapy (CRT) for small size HCC developed in cirrhotic liver and non suitable for curative therapies.
**Background:** Small size HCC benefit from curative therapies (liver transplantation, surgical resection or percutaneous destruction) while others are candidates for palliative options. Although liver conventional external radiation is regarded as little efficient and potentially toxic in cirrhotic patients (pts), 3D-conformal radiotherapy (CRT) for single HCC nodules demonstrated recent promising results.
**Materials and Methods:** A prospective phase 2 was conducted in 26 pts with small HCC (1 nodule $\leqslant$5 cm, or 2 nodules $\leqslant$3 cm) not suitable for curative treatment, Child-Pugh class A (15), B (8), 19 males, mean age 70, mean tumor size 3.2 cm. The aim was to assess the tolerance and efficacy of CRT (primary endpoint: rate of complete tumor response assessed by contrast-enhanced spiral CT scan showing disappearance of the arterial contrast enhancement on 2 successive examinations at 3 mo interval; secondary endpoint: toxicity assessment, using NCI then RTOG-EORTC Soma-Lent grading scales). CRT delivered 66 Gy (2 Gy/fraction, beam energy >10 MV). Tolerance was evaluated by using dose-volume histograms and normal tissue complication probability.
**Results:** Out of the 23 currently evaluable pts, 18 (78%) achieved a complete tumor response, maintained with time, and 5/23 no response (potential residual hypervascularisation but unchanged size of tumor). With a median follow-up of 17$\pm$8 mo, 2 pts relapsed on the irradiated tumor bed at 12 and 30 mo. No grade 4 toxicity was observed in 16 Child-Pugh A pts. Gr. 4 biochemical toxicity was observed in 2/9 pts Child-Pugh B (thrombocytopenia, hyperbilirubinemia), gr. 3 in 4 pts, 1 developed a gr. 3 portal hypertensive bleeding requiring transfusion, 1 pt a jaundice with edema and ascites at 1 mo, which spontaneously resolved.
**Conclusion:** This phase II trial showed for the first time in Europe that High Dose CRT can induce a complete tumor response maintained with time (local control) in 78% of pts presenting with small HCC nodules. Tolerance seemed to be better in Child-Pugh A pts than Child-Pugh B. This non invasive technique is highly suitable for tumors unreachable by percutaneous destruction. The current study (RTF2) evaluates the tolerance and efficacy of chemoembolisation followed by radiation for large lesions (>5 cm).

**3540** POSTER

**Postoperative adjuvant gemcitabine plus oxaliplatin (GemOx) chemotherapy followed by chemoradiation in patients with pancreatic carcinoma: mature results of a multicenter phase II study**

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The primary objective of this multicenter phase II non randomized study is to evaluate the overall survival rate, recurrence free 1-year survival rate, the time to disease progression and local recurrence rate for patients who have benefited from potentially curative surgery for pancreatic cancer, followed by an adjuvant chemoradiation regimen.
**Background:** Gemcitabine (Gem) has potential activity in advanced pancreatic cancer and is a powerful radiosensitizer. We evaluated the potential effectiveness and feasibility of postoperative GemOx chemotherapy followed by concurrent Gem and irradiation (RT) after curative resection for pancreatic adenocarcinoma.
**Materials and Methods:** Fifty-four patients with resected adenocarcinoma of the pancreas and negative resection margins (R0) were entered. Gem 1000 mg/m$^2$ over 100min on d1 then Ox 100 mg/m$^2$ (120min) on d2 were given (q2w for 6 cycles). After a 4-week rest period, Gem 100 mg/m$^2$ weekly combined with RT 50 Gy (2 Gy/fraction) were administered over 5 weeks in patients with no residual toxicity and no recurrence. Only patients who underwent both regimens are followed up to 24 months.
**Results:** The treated population (at least 2 induction cycles) included 49 patients (91%) with median age: 59.2 yrs; baseline Karnofsky performance status $\geqslant$80: 96%; stage T3/T4: 41%; lymph node positive: 43%; median time from surgery to inclusion was 43 days. Forty six patients (85%) received. the 6 planned induction cycles and 41 patients (76%) completed chemoradiation. The recurrence free 1-year survival rate is estimated at 71% (95% CI [0.581; 0 845]). Median dose intensity during induction: Gem 0.93, Ox 0.92, during chemoradiation: Gem 0.98. Forty one patients (98% of the irradiated population) received the total 50 Gy radiation dose.
The most frequent Gr 3/4 toxicities during induction chemotherapy (N = 51) were: hematological 29% (neutropenia 18%, thrombocytopenia 14%), nausea, vomiting, diarrhea:16%. Acute Gr 3/4 toxicities during chemoradiation (N = 42): neutropenia 19%, thrombocytopenia 7.0%. No toxic death occurred on treatment.
**Conclusion:** This adjuvant GemOx regimen combined with Gem-based chemoradiation was well tolerated during the two treatment phases with an encouraging 71% 1 year RFS. The late toxicities and OS will be analyzed after the end of the 2 years follow-up period. Mature results, will be presented during the meeting.