of the irradiated volume 12 months after treatment. Nine patients had new hepatic tumors, solitary in 1 patient and multiple in 8, exclusively outside the irradiated volume 4–29 months after proton beam therapy. Subsequently, 2 of the 10 patients with new hepatic tumors received second proton beam therapy and the irradiated new tumors were controlled. Consequently, all patients but one died 3–63 months after proton beam therapy; the causes of death were cancer in 6 patients, liver failure in 8, intracranial hemorrhage in 2, and interstitial pneumonitis and trauma in 1 each. The remaining 1 patient was alive with no evidence of disease 33 months after proton beam therapy. The overall and progression-free survival rates were 53% and 47% at 1 year, respectively, and 42% each at 2 years. Performance status and Child-Pugh score were significant prognostic factors for survival. Therapy-related toxicity of grade 3 or more was not observed.
Conclusions: Proton beam therapy for HCC patients with severe cirrhosis was effective and tolerable. It appeared to have achieved good local control and improved survival for the patients.

789 PUBLICATION

The FOLFIRI.3 regimen (5-FU/ folinic acid plus CPT-11) in advanced pancreatic carcinoma (PC): results of an AGEO* phase II study

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Background: New therapies are clearly needed to improve the prognosis of patients (pts) with advanced PC. The rationale to develop the FOLFIRI.3 regimen is based on pre-clinical experiments on cell cultures and human tumor xenografts indicating optimal synergy between CPT-11 and fluorouracil when CPT-11 is given before and after 5-FU.
Methods: 35 pts with non pre-treated locally advanced (LA) or metastatic (M) PC were prospectively enrolled. They received a FOLFIRI.3 regimen: CPT-11 90 mg/m* d1 and d3, folinic acid 400 mg/m* on a 2h00 infusion and continuous 5-FU 2000 mg/m* from d1 to d3. Treatment was repeated every two weeks until disease progression or limiting toxicity. Eligibility criteria were: pathologically proven PC, PS (ECOG) 0–2, age $\geqslant$18, measurable disease, serum bilirubin <1.5 UNL, adequate hematological and renal functions.
Results: 31 pts are currently evaluable for toxicity and 29 for efficacy. Patient's characteristics were M:18 pts/F:13 pts; LA:7 pts/ M:24 pts; mean age: 58 years (42–77) and initial performance status (WHO) was 0/1/2 in 8/14/9 pts, respectively. No Toxic death occurred. Hematological grade 3–4 toxicities consisted in neutropenia (32%), including two febrile neutropenia. Only 1 grade 3 thrombocytopenia (3%) and anemia (3%) were seen. Grade 3–4 non hematological toxicities were nausea vomiting (35%) and diarrhea (29%). Grade 2 alopecia was observed in 14 pts (45%). Eleven objective responses (35%) were observed, one leading to a surgical resection of the tumor. CA 19.9 decreased (>50%) in 56% of the patients with initially elevated CA 19.9. Nine (29%) stable disease and 9 PD (29%) were observed and 2 pts were not evaluable. With a mean follow-up of 9 months, median progression free and overall survival were 6.7 (CI:5–12.1) and 13.8 months (CI: 5.5–17.9), respectively.
Conclusion: With a 35% overall response rate and manageable toxicity the FOLFIRI.3 regimen seems to be an active regimen in non pre-treated advanced PC pts.

790 PUBLICATION

Neoadjuvant chemotherapy can eradicate lymph node micrometastasis for squamous cell carcinomas of the thoracic esophagus

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Background Data: Neoadjuvant chemotherapy has been postulated but not yet proved to eradicate micrometastasis and improve prognosis of patients with advanced squamous cell carcinomas of the thoracic esophagus (ESCC).
Cytokeratin immunohistochemistry of the lymph nodes of ESCC revealed not only Micrometastases (MM) but also Cytokeratin Deposits (CD), which are hyalinized and de-nucleated particles, considered to be the cadaver of carcinoma cells. Successful chemotherapy should convert cancer cells from MM to CD and ESCC patients from systemic disease to regional disease.
Methods: Cytokeratin immunostaining of surgically removed lymph nodes were performed for 100 patients with node-positive ESCC patients, including 25 patients treated with surgery alone (Surgery Group) and 75 patients undergone neoadjuvant chemotherapy using CDDP, Adriamycin and 5Fu (NACT group). Cytokeratin positive staining was referred to serial hematoxylin-eosin stained sections and classified as metastasis, MM and CD.
Results: CD was less frequently observed in Surgery group than in NACT group (8% vs 47%, $p = 0.0024$), while MM tend to be higher in the former (52% vs 40%). MM was a poor prognostic factor in both Surgery and NACT group, while CD was a favorable prognostic factor in NACT group. Effect of NACT on MM were considered to be eradicated: MM(−)/CD(+), persistent: MM(+)/CD(+), no effect: MM(+)/CD(−) and not informative: MM(−)/CD(−). This classification was well correlated with clinical response of main tumor, number of lymph node metastasis in the surgical specimen and post operative survival (3 year survival: 78%, 18%, 0% and 38% respectively). MM(−)/CD(+) was a significant prognostic factor as well as number of lymph node metastasis in the multivariate analysis.
Conclusion: Disappearance of MM and emergence of CD might suggest the eradication of MM by NACT. Clinical benefit of NACT was apparent for these patients with node positive ESCC.

791 PUBLICATION

A phase II study of gemcitabine and oxaliplatin in combination with celecoxib in patients with advanced pancreatic tumors overexpressing cyclooxygenase-2 (COX-2)

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Introduction: Overexpression of the COX-2 enzyme has been reported in 90% of patients with advanced pancreatic cancer.
COX-2 contribute to tumor growth through angiogenesis and may be implicated in gemcitabine and oxaliplatin resistance by increasing expresion of NK-kB.
Gemcitabine and oxaliplatin (GEMOX) is an active regimen in pancreatic cancer.
The aim of this study is to evaluate the activity and toxicity of GEMOX plus celecoxib in advanced pancreatic cancer.
Patients and methods: A phase II study according to Fleming regimen was used: 43 patients should be included to demonstrate an increase in response rate of 10% in comparison with the response obtained by GEMOX regimen (for an overall response rate of 40%).
Patients with metastatic and/or advanced disease were eligible for the study. All patients should have COX-2 by immunohistochemistry or cytochemistry.
Tumor response was assessed by RECIST criteria with CT imaging every 3 cycles. Ca 19–9, pain assessment and QoL assessment were performed every cycle.
The patients received gemcitabine 1000 mg/mq on day 1 and oxaliplatin 100 mg/mq on day 2 every 14 days. Celecoxib was administered at the dose of 400 mg/mq bid through the entire cycles.
Results: Forty-three patients (median age 57 years) were enrolled of which 15 local and 28 metastatic.
The most common grade 3/4 toxicities included: diarrhea 3/43, nausea and vomiting 4/43, neutropenia 5/43, and 3/43 peripheral neuropathy. A marked decrease in elevated baseline CA19.9 (>50%) was observed in 12 patients (27.9%). 13/43 (30.2%) patients reported an improvement in quality of life. Six patients achieved a partial response (13.9%) and 28 (65.1%) showed a stable disease. The overall median time to progression was 4 months and median survival was 9.5 months.
Conclusion: In conclusion, the addition of celecoxib does not seem to increase the activity even in tumors overexpressing COX-2.

792 PUBLICATION

Preliminary results of a phase II trial of dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma

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Background: PEFG regimen was superior to standard gemcitabine in a phase III trial (Reni M Lancet Oncol 2005) in advanced pancreatic adenocarcinoma (PA). This regimen was subsequently modified by increasing dose-intensity (Dell'Oro S, Ann Oncol 2004). The aim of the present study was to assess activity and feasibility of dose-intense PEFG regimen.

Material and methods: 5-fluorouracil (FU) as continuous infusion at 200 mg/m^2/day for the whole duration of chemotherapy, cisplatin and epirubicin both at 30 mg/m^2, and gemcitabine at 800 mg/m^2 were administered every 14 days to patients with stage III or metastatic pancreatic adenocarcinoma who were chemotherapy-naive, ⩽75 years, performance status >50, and who had normal bone marrow, renal and liver function, till progressive disease (PD) or for a maximum of 6 months. Analyses were conducted in the intent to treat population.
Results: Between August 2003 and April 2005, 43 (27 or 63% metastatic) consecutive patients, median age 62 years, median performance status 75, were treated with dose-intense PEFG at a single institution. Accrual is ongoing. Partial response was yielded in 18 patients (42%). Among 33 patients with at least 6 months of follow-up, 18 were progression-free at 6 months from treatment start (PFS-6 = 54.5%) and median progression-free survival was 6.2 months. Three of 16 (18%) stage III patients became resectable after chemotherapy and were submitted to surgery. Radiotherapy concomitant to FU was administered to 10 stage III patients after the end of PEFG chemotherapy. To date, 169 courses (range 1–6, median 4) of dose-intense PEFG were delivered. Treatment is ongoing in 6 patients. Main grade 3–4 toxicity consisted of: neutropenia in 9%, anaemia, stomatitis, nausea/vomit in 3%, fatigue and diarrhoea in 2% of cycles. No grade >2 thrombocytopenia was observed. Dose intensity (mg/m^2/week) was 13.5 for both epirubicin and cisplatin, 322 for gemcitabine and 1053 for FU.
Conclusion: Preliminary results of this study show that the outcome of patients with PA treated by dose-intense PEFG regimen is at least as good as that yielded by classical PEFG in terms of PFS (PFS-6: 54.5% vs. 42%; median PFS 6.2 vs. 5.4) and response rate (42% versus 38.5%). With respect to classical PEFG, dose intensity of gemcitabine was increased by 26% and dose intensity of cisplatin and epirubicin by 43%. Grade 3–4 hematological toxicity was consistently reduced (neutropenia 9% vs. 43%; thrombocytopenia 28.5% vs. 0%).

793 PUBLICATION

Salvage therapy with bevacizumab, capecitabin, and mitomycin C (BECAM) for patients with metastatic colorectal or gastric cancer refractory to 5-fluorouracil, oxaliplatin, irinotecan, and cetuximab

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Background: Bevacizumab has been shown to improve efficacy when combined with irinotecan and 5-FU based chemotherapy in chemonaïve patients (pts) as well as in combination with oxaliplatin in refractory pts with metastatic colorectal cancer (mCRC). This study was designed to explore BECAM, the combination of Bevacizumab together with the oral 5-FU prodrug Capecitabin and Mitomycin C (MMC), concerning tolerability and activity in heavily pretreated pts with mCRC or gastric cancer (GC).
Methods: BECAM consisted of a 1-hour-infusion of Bevacizumab [7.5 mg/kg] in addition to a previously reported schedule from our group consisting of of bolus-injection of MMC [7 mg/m^2], and Capecitabin [2 × 1000 mg/m^2/day] taken twice daily from day 1–14. All medication was repeated from day 21 on.
Results: 16 pts with mCRC (n = 13) or GC (n = 3) were enrolled: 6/10 m/f, median age 62 years [41–76], median Karnofsky PS 80% [70–100]. Median number of previous chemotherapy regimen was 3 (range 2–6). All mCRC pts had received prior cetuximab.
Median duration of treatment was 3 cycles [1–6]. 15 pts were evaluable for toxicity: Main grade 3/4 toxicities were thrombocytopenia (3/15 pts), hypertension, and haemorrhage (1/15 pts each), of which only the bleeding episode was severe and caused cessation of Bevacizumab therapy. Thrombocytopenia, as known from MMC therapies, was the most common side-effect (8/15 pts ⩾grade 2) leading to treatment delay in 40% of the cases (6/15 pts).
By contrast, sympomatic toxicities were rare and restricted to grade 1 with only one episode of grade 2 nausea. There was no allergic reaction to any of the substances used.
Efficacy analysis of 13 pts (3 too early) revealed partial remission (PR) in 2 pts (1 with GC and 1 with mCRC), and diseaser stabilisation (SD) in 5/13 pts (4 CRC and 1 GC) leading to a tumor control rate of 54%. 6/13 pts progressed early on treatment.
As expected in this stage of anticancer treatment, duration of response, if any, was rather short, resulting in a median PFS of 2.5 [2–7] months, and an OS of 3.5 [3–9] months.
Conclusions: Although patient numbers in this study were small, BECAM seems to be a regimen with a favourable toxicity profile and considerable activity in this group of heavily pretreated pts with mCRC or GC. Toxicity was generally mild and did not affect patients' quality of life. However, as known from preceding studies with Bevacizumab, rare events of specific toxicity, in this case grade 4 haemorrhage, may be life-threatening.

Genitourinary Cancer

Oral presentations (Thu, 3 Nov, 8.30–10.30)
GU – Kidney and testis cancer

794 ORAL

Randomized Phase III trial of the multi-kinase inhibitor sorafenib (BAY 43–9006) in patients with advanced renal cell carcinoma (RCC)

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Background: Sorafenib (BAY 43–9006), an oral multi-kinase inhibitor with effects on the tumor and vasculature, was shown in a Phase II trial to have anti-tumor activity in patients (pts) with metastatic RCC. The primary aim of this Phase III, double-blind, placebo-controlled trial was to assess the effects of sorafenib added to best supportive care (BSC) on overall survival (OS) in pts with confirmed, advanced clear-cell RCC.
Patients and Methods: Pts (ECOG PS 0–1) who had failed one prior systemic therapy for advanced RCC were stratified according to low or intermediate Motzer prognostic factor, and randomized to receive continuous oral sorafenib 400 mg bid or placebo with BSC. The primary endpoint was OS. Secondary endpoints were progression-free survival (PFS) (single, planned analysis after 363 progressions), best response (RECIST), health-related quality of life (HRQOL) and symptom response. Adverse events (AEs) were recorded by CTCAE v3.0.
Results: 905 patients have been randomized. The first interim analysis on 769 pts has been recently reported. Baseline characteristics for all 769 pts were: mean age, 58 yrs; ECOG 0:1, 47%:51%; Motzer prognostic factor low:intermediate, 51%:49%; prior cytokine therapy, 82%; prior nephrectomy, 93%. These were similar between treatment groups. Following a study modification to allow pts to cross from placebo to sorafenib, monitoring is continuing for OS analysis (to be reported at time of presentation). Median PFS (independent review) was 24 weeks for sorafenib and 12 weeks for placebo (hazard ratio sorafenib/placebo, 0.44; $p < 0.000001$). At 3 months post-randomization, 75% of pts on sorafenib were progression free versus 43% of those on placebo. Changes in tumor vascularization, as assessed by Color Doppler ultrasonography, were highly predictive of PFS and OS. A statistical significant difference of observed mean changes between treatment arms in the PWB of the FACT-G and FACT-KSI-10 scores over time was seen. Drug-related AEs (sorafenib:placebo) included rash/desquamation (31%:11%), diarrhea (30%:7%), hand–foot skin reaction (26%:5%), and hypertension (8%:<1%). Fatigue (18%:14%) was not significantly different between sorafenib and placebo. No significant biochemical toxicity was observed.
Conclusions: Sorafenib significantly prolongs PFS compared with placebo in pts with previously treated advanced RCC, and is well tolerated with manageable side-effects. Full data will be presented at the meeting.

795 ORAL

Phase II trial of sorafenib (BAY 43–9006) in combination with interferon alpha 2b in patients with metastatic renal cell carcinoma

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Background: Sorafenib (BAY 43–9006) is a novel, oral multi-kinase inhibitor that acts on Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR-β to mediate effects on the tumor and vasculature. In Phase II/III trials, sorafenib significantly prolonged progression-free survival (PFS) versus placebo, and had a favourable safety profile in patients with renal cell carcinoma (RCC). This Phase II, multicentre, open-label study was designed to determine the tolerability and response rate (RECIST) of sorafenib in combination with interferon (IFN) alpha-2b in patients with metastatic RCC. Secondary endpoints were PFS, response duration and overall survival, as well as changes in tumor NFκB, ERK, and VEGFR-2 activation and apoptotic protein expression.