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.

Patients and Methods: Patients with locally advanced or metastatic RCC, who may have received radiation therapy and/or one biologic response modifier regimen, were enrolled. Patients received 8-week cycles of continuous oral sorafenib 400 mg bid with subcutaneous IFN alpha-2b 10 MIU tiw. Patients continued to receive treatment until disease progression, unacceptable toxicity or death. To resolve toxicities, a 2-week treatment break between cycles was permitted.
Results: Fourteen of a planned 40 patients were enrolled. Patients' characteristics were: median age 58 years (range 33–81); ECOG 0:1, 86%:14%; prior therapy, 64%; prior IL-2, 50%; prior nephrectomy, 93%; ⩾2 metastatic sites, 50%; clear-cell histology, 71%. Of the eight patients evaluable for tumor response after Cycle 1, three patients had a partial response, one patient had a minor response and three patients had stable disease. Three of the responders had failed prior IL-2. Five patients experienced dose-modifying toxicities of grade 2 fatigue (n = 2), diarrhea or hypoalbuminaemia (n = 1 each), grade 3 rash (n = 2) or abnormal AST/ALT (n = 1), and grade 4 neutropenia (n = 1). Frequent toxicities included grade 1/2 fatigue/depression (n = 9), rash (n = 5), diarrhea (n = 3), hypophosphataemia and nausea/vomiting (n = 2 each). Grade 3/4 events included rash (n = 2), elevated lipase, leukopenia, neutropenia and hypophosphataemia (n = 1 each).
Conclusions: Oral sorafenib 400 mg bid plus IFN alpha 2b 10 MIU tiw shows preliminary evidence of anti-tumor activity both in untreated patients and in IL-2 failures, and appears to be safe and well tolerated in patients with metastatic RCC. Further data, including the effects on signaling in tumors, will be updated at the meeting.

796 ORAL

Bevacizumab, erlotinib, and imatinib in the treatment of patients (pts) with advanced renal cell carcinoma (RCC): Update of a Minnie Pearl Cancer Research Network phase I/II trial

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Background: The overexpression of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) in renal cell cancer (RCC) provides rationale for combining novel biologic agents which inhibit these receptors. In a prior multicenter phase II trial, combined VEGF/EGF receptor inhibition with bevacizumab and erlotinib was an active and safe regimen for pts with metastatic RCC. In this phase I/II trial, we added imatinib, which targets PDGF expression, to bevacizumab/erlotinib.
Methods: Eligibility: metastatic clear cell RCC, 0–2 previous systemic regimens, ECOG PS 0–1, no previous anti-angiogenesis or EGF receptor inhibitor therapy, no active CNS metastases, adequate organ function, no history of thromboembolic disease, informed consent. All pts received bevacizumab 10 mg/kg IV q 2 weeks, and erlotinib 150 mg po daily. In the phase I portion of the trial, imatinib levels were escalated: 300 mg qd (cohort 1), 400 mg qd (cohort 2), and 600 mg qd (cohort 3). Pts were evaluated for response after 8 weeks using RECIST criteria; treatment continued until tumor progression.
Results: In the phase I portion of the trial, imatinib 400 mg qd was identified as the maximum tolerated dose. At this dose level, 2 of 10 patients had reversible dose-limiting toxicity (diarrhea). Between 7/04 and 3/05, 91 pts were treated. This report contains preliminary results on the first 48 patients entered (44 evaluable). Pt characteristics included: median age 63 years; male/female, 37/11; ECOG 0/1, 14/34; 34 pts (71%) were previously untreated; the remainder had received IL-2 and/or interferon. Four of 44 evaluable pts (9%) had objective responses (all PR). Twenty-seven pts (61%) had stable disease; however, 6 of these pts (14% of total) had minor objective responses (10–30% decrease by RECIST criteria). Progression-free and overall survivals at 9 months are 66% and 70%, respectively. The median duration of follow-up is 5 months (range 3–10 months). Grade 3/4 toxicity: diarrhea 29%; rash 27%; nausea/vomiting 13%; hypertension 2%; bleeding 2%; proteinuria 2%; fatigue 6%.
Conclusions: The combination of bevacizumab, erlotinib, and imatinib is active in pts with metastatic RCC. Although tolerable for most patients, imatinib appears to increase the frequency and severity of diarrhea, rash, and fatigue. Further follow-up of the entire 91 patients on this trial is necessary prior to making final conclusions regarding this combination regimen. Updated results on the entire group of 91 pts will be presented.

797 ORAL

Sunitinib malate (SU11248) shows antitumour activity in patients with metastatic renal cell carcinoma: updated results from phase II trials

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Background: In clear cell renal cell carcinoma (RCC), loss of VHL gene function results in up-regulated expression of VEGF and PDGF. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor of VEGFR and PDGFR and has demonstrated both antiangiogenic and antitumour activities in phase I trials in RCC and other tumour types. Therefore, we evaluated the antitumour activity and safety of sunitinib in patients (pts) with metastatic RCC in two independent single-arm, phase II trials.
Patients and methods: Eligibility for both trials included measurable disease, failure of one prior cytokine therapy, ECOG PS of 0/1, and adequate organ function. Pts received sunitinib 50 mg q.d. orally for 4 weeks, followed by 2 weeks off treatment to comprise a cyclical 6-week regimen. Best response was assessed using RECIST.
Results: Trial 1 enrolled 63 pts (Jan 03 – Jul 03) and Trial 2 (ongoing) enrolled 106 pts (Feb 04 – Nov 04). Best responses for evaluable pts are shown in Table 1 and are presented as of Apr 05.

Table 1. Best response to sunitinib in RCC pts.

	Objective response N (%)	CR N (%)	PR N (%)	SD ⩾3 months N (%)	PD or SD <3 months N (%)	Not evaluable N (%)
Trial 1 (N = 63)	25 (40)	0 (0)	25 (40)	18 (29)	16 (25)	4 (6)
Trial 2 (N = 106)*	42 (40)	1 (1)	41 (39)	24 (23)	33 (31)	7 (7)

*Study ongoing

Of 25 pts who achieved a PR in Trial 1, the median duration of response is 12.5 months (range 2–19+). The median TTP is 8.7 months and median survival is 16.4 months. Currently, 8 PRs are progression-free at 21+ to 24+ months (from start of therapy), including 6 pts remaining on therapy and 2 rendered disease-free by surgery. In Trial 2, of 24 pts with best response of SD, 5 had tumour reduction of 30% and await confirmation of response status. Overall, the majority of treatment-related adverse events and haematological abnormalities were grade 1 and 2, and included (Trial 1, Trial 2): fatigue (38%, 22%), diarrhoea (24%, 16%), stomatitis (19%, 14%), neutropenia (45%, 39%), anaemia (37%, 25%), and thrombocytopenia (18%, 19%).
Conclusions: Two consecutively conducted phase II trials demonstrate that sunitinib has substantial antitumour activity in pts with metastatic RCC. The objective response achieved in Trial 1 (40%) was confirmed independently in Trial 2 (40%). Sunitinib has manageable adverse events, with responding pts receiving treatment for over 2 years. Further studies to explore sunitinib as first-line therapy are underway.

798 ORAL

A prospective study of 18FDG PET in the prediction of relapse in patients with high risk clinical stage I non-seminomatous germ cell cancer (MRC study TE22)

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Background: Optimum management of patients with clinical stage I (CS1) non-seminomatous germ cell tumours (NSGCT) has been debated; options include adjuvant chemotherapy, retroperitoneal lymph node dissections (+/− adjuvant chemotherapy) and initial surveillance with treatment at relapse. Each approach achieves similarly high cure rates (>98%).