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%).

Surveillance is attractive option, avoiding unnecessary treatment, but would be even more attractive if a greater proportion of patients with occult metastatic disease could be identified and administered earlier, potentially less toxic, treatment.
A Danish pilot study in CS1 NSGCT showed that FDG PET could identify 70% of patients who subsequently relapsed, and had a negative predictive value of 90%. If confirmed this would suggest that further treatment could be avoided in most patients with CS1 NSGCT and negative PET scans.
Methods: NSGCT patients judged to be CS1 based on markers and CT, and high risk based on vascular invasion, were registered within 8 weeks of orchidectomy, and underwent an 18FDG PET scan. Following a positive scan, patients went off study and could be managed according to local protocols. Patients with negative scans were followed on surveillance. The primary outcome measure was the negative predictive value of the PET scan, defined as the 2-year relapse-free rate in patients with a negative PET scan. This was expected to be approximately 90%, and to exclude rates below 80% with 80% power, at a 5% significance level, approximately 100 PET negative patients were required and we anticipated scanning 135 patients to achieve this.
Results: Patients were registered between May 2002 and January 2005. At this time, when 116 patients were registered and PET scan results were available on 96 patients (78 PET –ve, 18 PET +ve), an independent Data Monitoring Committee review lead to early closure of the trial, due to an unacceptably high relapse rate in the PET-ve patients. PET +ve patients were slightly older than PET –ve patients (35 vs 29 yrs) and more likely to have MTU histology (83% vs 46%) and/or to have normal markers pre-orchidectomy. All PET +ve patients were scheduled for adjuvant BEP chemotherapy. One PET –ve patient requested adjuvant chemotherapy. Of the remaining 77, 23 relapsed leading to a one-year relapse-free rate of 65% 90% CI (53%, 74%). The maximum 2 year relapse-free rate (assuming complete follow-up and no further relapses) would be 70% (60%, 79%).
Conclusions: Though PET identified a proportion of patients with disease not detected by CT scan the relapse rate amongst PET –ve patients remains high. The study results therefore suggest that 18FDG PET scanning is not able to identify patients at sufficiently low risk of relapse to replace other treatment options in this setting.
This study was supported by Cancer Research UK

799 ORAL

Gonadal hormones, sperm counts and post-treatment paternity in long-term survivors of unilateral testicular cancer

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Background: In long-term survivors of unilateral testicular cancer (TC) post-treatment serum follicle-stimulating hormone (s-FSH), serum testosterone (s-tes) and sperm counts were analysed according to previous treatment and associations with post-treatment paternity were assessed.
Material and methods: In 1998–2002 TC patients treated 1980–1994 in Norway were followed-up by a questionnaire, clinical examination and laboratory assessments. Of 1687 eligible men under 65 years without androgen replacement, serum hormones were analysed in 1198 (median follow-up 11 years, age 43 years). 348 delivered a semen sample. Patients were grouped according to treatment: Surgery only (Surg, n = 236), radiotherapy only (RT, n = 487), and two chemotherapy groups, [Cisplatin (Cis) $\leqslant$850 mg, n = 385 and Cis >850 mg, n = 90].
Results: S-FSH was elevated ($\geqslant$12 IU/l) in 42% of the men: Surg, 31% (median 8.8 IU/l); RT, 37% (9.7 IU/l); Cis $\leqslant$850 mg, 47% (11.1 IU/l) and Cis >850 mg, 77% (20.2 IU/l) ($p < 0.001$). In a linear regression model, age, cryptorchism and treatment group were significant factors for logarithmic s-FSH ($p < 0.001$), but with no difference between the RT and Surg group. In a linear regression model including age ($p < 0.001$) and cryptorchism ($p = 0.14$), s-tes was significantly lower in all treatment groups compared to Surg ($p = 0.02$). Sperm counts were <20 mill/ml in 49%, and <10 mill/ml in 36%. The frequency of azoospermia varied from 10% (Surg) to 43% (Cis >850 mg). In a proportional ordinal logistic regression for increasing levels of sperm counts (0, 0.1–1.9, 2.0–9.9, 10.0–19.9 and $\geqslant$20 mill/ml), adjusting for age and cryptorchism, the odds ratios compared to surgery were: RT, 0.74 (95% CI 0.43–1.27); Cis $\leqslant$850 mg, 0.51 (95% CI 0.29–0.89); and Cis > 850 mg, 0.20 (95% CI 0.08–0.52). Overall, 488 had tried to conceive a child following treatment. The median s-FSH value was 8.7 IU/l in those who succeeded (n = 330) vs. 12.8 IU/l in those who failed (n = 157) ($p < 0.001$). Respective s-tes values were 15.2 vs. 14.2 mmol/l (NS) and median sperm counts were 32 vs. 4.2 mill/ml ($p = 0.004$). In a Cox regression model where logarithmic s-FSH, s-tes and cryptorchism were assessed for their association with post-treatment paternity, only s-FSH remained an independent factor ($p < 0.001$). In men whose semen was analysed, both sperm count and s-FSH ($p = 0.03$) were significantly associated with post-treatment paternity.
Conclusions: Post-treatment spermatogenesis evaluated by post-treatment s-FSH and sperm counts was impaired in 42–49% of long-term survivors of TC and was associated with paternity after treatment. RT did not significantly impair long-term spermatogenesis compared to surgery, whereas chemotherapy did, with more severe suppression at the higher doses. Cytotoxic treatment significantly reduced s-tes as compared to surgery alone, but no association was observed between post-treatment paternity and s-tes.

Oral presentations (Tue, 1 Nov, 9.15–11.15)
GU – new frontiers in genitourinary cancers

800 ORAL

Molecular prognostic markers for survival after chemotherapy in advanced bladder cancer

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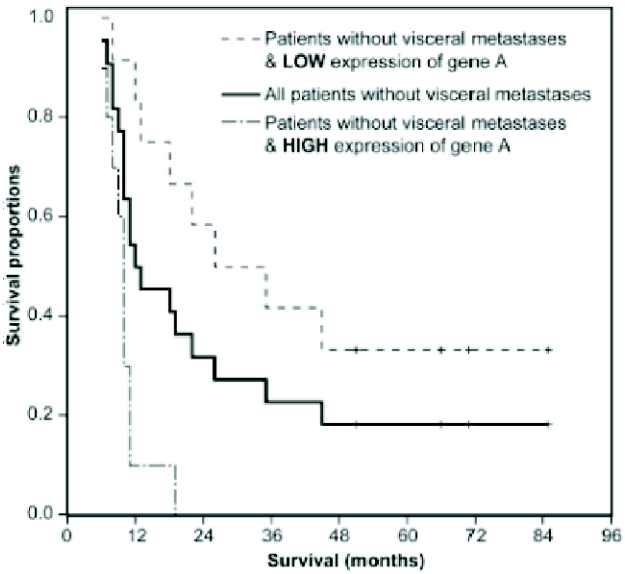
Background: In patients with advanced bladder cancer, cisplatin-containing chemotherapy yields response rates around 50%, with a median survival around 12 months. Poor performance status (PS $\geqslant$ 2) and presence of visceral metastases are identified as independent poor prognostic factors for survival in several studies. However these factors are not strong enough to predict the outcome for the individual patient.
Aim: To identify differentially expressed genes with a prognostic impact on survival after the cisplatin-containing regimens MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin).
Material and methods: We identified 31 patients with a follow-up time of more than 15 months following MVAC or GC. Tumor biopsies were sampled less than four months prior to chemotherapy. Gene expression data were generated using Affymetrix GeneChip HU133A. Genes that correlated significant with survival were identified using SAM (Significance Analysis of Microarrays; Stanford University Labs).



Survival of patients with advanced urothelial cancer without visceral metastases according to expression values of gene A.

Results: Thirty-nine genes correlated highly significantly with survival. We selected five genes well annotated and with intelligible biological relevance for further analyses. The genes encode proteins involved in apoptosis regulation, DNA-damage-repair upon chemotherapy, cell-proliferation and angiogeneses. Expression values were dichotomized and analyzed in combination with clinical prognostic factors. Patients with (n = 9) or without