disease specific survival for the patients with de novo muscle invasive tumour was 60%, whereas it was 38% for patients with initially superficial tumour progressing to muscle invasive disease (p=0.003). The median time from the initial diagnosis until cystectomy varied significantly with minimal delay in group I with 52 days (range, 5 days 8.4 years) and maximum delay in group II with 1 year (range, 8 months - 23.6 years) (p<0.001). However, the median time from the first muscle invasive diagnosis until cystectomy was 52 days for group I and 39 days (range, 0-6.8 years) for group II.

Multivariate analyses, including all patients, revealed that patients with N+, non-organ confined tumour and with initial superficial disease progressing to muscle invasive tumour were independent poor predictors of death of bladder cancer.

Conclusion: These data showed that the proportion of patients with superficial tumours, which progressed despite of close follow up and intravesical therapy had a significant poorer outcome following radical cystectomy compared to patients with de novo muscle invasive tumours. Therefore early identification and early cystectomy of patients with high-risk superficial tumours are suggested.

1098 ORAL

Phase III study of neovastat in metastatic renal cell carcinoma patients refractory to immunotherapy

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Cytokines remain the first-line treatment for renal cell carcinoma (RCC). For patients with progressive disease following initial therapy, no standard treatment is available, and new approaches are needed. Neovastat is a naturally occurring antiangiogenic oral drug with pleiotropic properties. No dose-limiting toxicity was observed in pre-clinical and Phase I/II clinical studies. In addition, a phase II trial in RCC patients showed a statistically longer median survival time in patients receiving 240 ml/day vs. 60 ml/day (16.3 months vs. 7.1 months, p = 0.01) (Batist et al., *Ann Oncol 2002;13:1259-63*). Based on these results, a prospective, randomized, double-blind, placebo-controlled phase III trial was conducted to determine the efficacy of Neovastat as monotherapy in metastatic RCC patients who had progressed following a first-line of immunotherapy.

Protocol: Eligibility criteria consisted of unresectable metastatic RCC, measurable disease, progressive disease after immunotherapy, and adequate bone marrow, hepatic and renal functions. Patients were stratified according to ECOG performance status (0 vs. 1) and number of metastatic sites (1 vs. >1) and were randomized in a double-blind fashion to Neovastat (120 ml B.I.D.) or placebo (ratio 1:1). The primary endpoint was median survival time and statistical hypothesis was improvement from 8 to 12+ months. Time to progression, one-year survival rate, quality of life, overall tumor response rate and duration of response were secondary endpoints.

Preliminary results: From May 2000 to January 2002, 302 patients were recruited in 46 centers (Argentina, Canada, Europe and USA). Median age was 61 years (25 to 81) with 75% (222) males and 25% (80) females. Fifty-two percent (52%) of the patients had ECOG 0. Seventy-five (75) patients had metastases restricted to one site. 227 patients had more than one metastatic site (lung, 70%; liver, 25%; bone, 29%). The safety profile of Neovastat appears acceptable and demonstrated no severe toxicity in either arm according to an independent Data Safety Monitoring Board review.

Conclusion: This study will provide key data on survival of patients with refractory RCC and will provide insights on the clinical activity of Neovastat. Mature data will be presented at the meeting.

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A phase II study of ABR-214936 (anatumomab mafenatox) tumour targeted superantigen (TTS) therapy in patients with advanced renal cell carcinoma (RCC)

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Tumour Targeted Superantigen (TTS) therapy is a novel form of cancer therapy. The principle involves targeting of the superantigen with strong activation of cytotoxic T cells in the tumour tissue. ABR-214936 (anatumomab mafenatox) is a recombinant fusion protein of a mutated Staphylococcal enterotoxin A (SEA) and a Fab moiety recognising the oncofetal antigen, 5T4, which is expressed in the majority of patients with RCC.

In this open non-controlled phase II study patients with confirmed RCC, measurable disease and good performance status are treated with a daily 3-hour infusion of ABR-214936 for 4 consecutive days. Pre-formed circulating anti-SEA antibodies neutralise the effects of ABR-214936 and therefore dosing is adapted to the pre-existing antibody-titre. Each patient is treated with an individual dose based on the pre-treatment anti-SEA antibody concentration and adjusted to body weight. A second cycle is given 4-6 weeks later at which the dose is adjusted to the new anti-SEA titre. Patients are evaluated by means of a pre-treatment CT scan with repeat scan at D56 and D112 to evaluate tumour response. If there is response then a 3rd cycle may be given.

Side effects observed include pyrexia, rigors, nausea and vomiting, and hypotension. If a patient experience a drug-related AE/SAE then the dose for the next infusion is decreased to 75% of that previously given, if there is a further reaction then the dose is reduced to 50% of the original. Treatment is well tolerated with only one patient withdrawn due to toxicity (grade 3 hypotension in first cycle). In cycle one 30% (12/43 pts) required a dose reduction due to grade 1 or 2 toxicity and only one patient required a dose reduction in the second cycle of treatment.

To date 39 patients out of 45 have reached D112 evaluation. The patient with maximum response has achieved a reduction in the measured size of the lesions by 90% after 3 cycles (PR by RECIST criteria on CT scan). This patient received ABR-214936 as second-line treatment. Approximately 36% of the evaluable patients have SD or better at the 4 month assessment. 4 patients have received 3 cycles of treatment

ABR-214936 is a promising and active agent in advanced RCC. It has been demonstrated to be safe and well tolerated. The study has now fully recruited and follow-up is ongoing.