changes and the occurrence and distribution of tumour-infiltrating mononuclear cells.

Results: Among patients with regional disease, 50% showed a high degree of regressive changes (more than 75 percent of the section area) after biochemotherapy. Patients with histopathological response could be identified pretreatment by analysing the numbers of tumour infiltrating CD4+ lymphocytes in FNA. There was a statistically significant correlation between the occurrence of these cells and a high degree of regressive changes post treatment, p=0.01. A Kaplan-Meyer analysis of patients with regional metastses showed a tendency to a longer overall survival in patients with a high degree of regressive changes. Similar results were found in a smaller group of patients with systemic disease.

Conclusion: Biochemotherapy showed a remarkable efficacy with a high degree of tumour regression in 50% of the patients with regional disease. There was a close correlation between extensive regressive tumour changes and the amount of tumour infiltrating CD4+ lymphocytes pre-treatment. Patients with regressive changes of more than 75% of the analysed biopsies were also found to have a tendency to a longer overall survival. Thus immunohistochemical analysis of tumour biopsies shortly after immunotherapy seems to be a good surrogate endpoint and this technique also allows a detailed analysis of anti-tumour reactivity and escape mechanisms.

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Immunomagnetic detection of micrometastatic cells in bone marrow predicts survival of patients with malignant melanoma and osteosarcoma

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Purpose: We have previously reported simple and sensitive methods for detection and characterization of micrometastatic tumor cells, based on the use of immunomagnetic and fluorescent microparticles. The aim of this work was to relate results obtained with our method on samples from patients with advanced malignant melanoma and with osteosarcoma to clinical parameters to examine the clinical potential of the method for predicting prognosis.

Methods: The methods were used on blood and bone marrow samples obtained from 152 melanoma patients and from 39 patients with primary osteosarcoma. Twentyfive (16.3%) melanoma patients had positive samples. This group showed a significantly shorter survival, both from primary operation (p = 0.031) and from time sampling (p = 0.042), than those without micrometastasis. Multiple variat analysis revealed that presence of melonoma cells was, together with the number of metastatic sites, the most important parameter of survival. In osteosarcoma, 50–100% of 39 patients had tumor cells in their bone marrow, increasing with disease stage. In a number of the patients the findings in repeated samples correlated to the effect of preoperative chemotherapy. The malignant nature of the immunomagnetically selected cells could be confirmed by binding of fluorescent antibody-coated particles targeting other tumor-associated antigens, and in a few cases by culturing the cells in vitro and in nude mice.

Conclusion: The results demonstrate the validity and clinical potential of using these methods for prognostication and response monitoring in these type of malignancies.

110 ORAL

Sentinel node biopsy improves regional node staging in melanoma patients

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Elective lymph node dissection (ELND) has been performed widely in the past for patients with melanoma who have been considered to be at high risk for local or systemic recurrence. Sentinel node biopsy (SNB) has largely replaced this technique in many major cancer centres in order to reduce postoperative morbidity and to minimise unnecessary dissections. Whether SNB, with subsequent lymph node dissection when micrometastatic disease is found in a SN, has any benefit in terms of survival remains unclear. Whilst some SNs are not removed due to technical failures, SNB has been shown to improve staging in breast cancer patients when compared to standard axillary lymphadenectomy. In melanoma patients such an improvement has never been demonstrated, therefore a large matched-paired patient study was conducted to compare nodal staging accuracy and survival in patients treated with either SNB or ELND.

All patients treated at the Sydney Melanoma Unit (SMU) between 1983 and 2000 for a primary tumour ~ 1.5 mm in thickness and who underwent a SNB (n=775) or an ELND (n=1026) were evaluated. Two groups of 659 ELND and 659 SNB patients treated over the same time period were matched for age, sex and thickness of the primary melanoma, and compared for node involvement.

The most important predictors of node positivity in multivariate analysis of the matched pairs were tumour thickness (p<0.0001), ulceration (p=0.001), and age (p=0.002). The overall number of patients with positive nodes after ELND was 11.4% and after SNB 16.1%, which was a statistically significant difference (p=0.004). Overall survival after 3 years of follow-up was comparable for both groups.

Thus it is concluded that SNB identifies proportionally more lymph nodes containing metastatic melanoma than ELND in this retrospective matched-paired cohort analysis. Detailed pathological examination, recent improvements in immunohistochemical techniques and accurate identification of the lymph node field(s) by preoperative lymphoscintigraphy are all likely to be responsible for this increased accuracy. Irrespective of any effects on survival which may be demonstrated by presently ongoing clinical trials, SNB in combination with preoperative lymphoscintigraphy is desirable for all patients entering trials of adjuvant therapy in order to create more closely equivalent patient groups.

111 ORAL

Histamine dihydrochloride administered with Interleukin-2 increases survival duration in patients with ocular melanoma with liver metastases

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Background: Ocular melanoma (OM) is the most common intra-ocular malignancy, and it metastasizes to the liver in about two-thirds of patients (pts). This portends a poor prognosis and a median survival of only 2 to 7 months. Therapy for metastatic cutaneous melanoma (CM) has been largely ineffective in pts with OM, and these pts are usually excluded from clinical trials for metastatic CM. Results of a large, randomized phase III trial of a novel combination of IL-2 and histamine dihydrochloride (HDC) compared with IL-2 alone have recently been reported [Agarwala et al. Cancer Invest 19 (suppl 1): 81, 2001], and a significant survival benefit in pts with melanoma metastatic to the liver treated with the combination of HDC and IL-2 was noted. Methods: To examine the potential role of IL-2 and HDC specifically in pts with OM with liver metastases (OM-LM), a retrospective analysis of 35 pts with OM-LM enrolled in a randomized trial and in on-going phase II trial of combination IL-2 and HDC was performed. Pts received IL-2 (9 MIU/m2, bid, sc, days 1-2, weeks 1,3; and 2 MIU/m2, bid, sc, days 1-5, weeks 2, 4) with or without HDC (1.0 mg, bid, sc, days 1-5, weeks 1-4) for 4 weeks of a 6-week cycle. Results: 13 pts received IL-2 alone, and 22 pts received the combination of IL-2 and HDC. In the group receiving HDC + IL-2, the median age was 55 years (range 31-79), 7 (32%) pts were male, and high LDH levels (> ULN) were present in 6/15 (40%) pts. In the group receiving IL-2 only, median age was 64 years (range 25-75), 9 (69%) pts were male, and high LDH levels were present in 6/12 (50%) pts. The median survival for pts with OM-LM receiving IL-2 + HD was 229 days compared to 119 days for pts receiving IL-2 alone (p=0.0051). Conclusions: These results suggest that the benefit noted for pts with CM metastatic to the liver in the randomized phase III trial of IL-2 + HDC vs IL-2 alone was not restricted to CM but extended to those with OM-LM. Further trials in this subset of patients are planned.

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Early evaluation of tumour response to STI 571 with FDG-PET in patients with soft tissue sarcomas (STS)

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Evaluation of treatment response is currently based on changes in tumour volume measured on CT. New anti-cancer drugs often induce tumour growth

arrest rather than tumour cell kill and thus early major changes in tumour volume are not to be expected. Assessment of tumour metabolic rate by PET has been suggested as an alternative end point for tumour response to therapy.

The **aim** of this study was to evaluate FDG-PET as an early metabolic response marker.

Methods: All patients (pts), included in EORTC phase I/II studies with STI 571, who underwent PET imaging prior to the start of treatment were included. All pts had histiological evidence of STS with documented progressive disease (PD). PET was performed prior to and 8 days after the start of treatment. PET consisted of an attenuation-corrected whole body scan acquired 1 hour after injection of FDG. Images were interpreted visually to assess the presence of new lesions and FDG uptake in target lesions was quantified (SUV_{max}). Four categories of metabolic tumour response (PD_{PET}, SD_{PET}, PR_{PET}, CR_{PET}) were defined based on the PET EORTC recommendations (*Young et al. Eur J Cancer 1999 1773–82*). Response on PET was correlated with subjective symptom control as well as objective tumour response evaluated on serial CT scans (RECIST criteria) acquired prior to and every 4 weeks after the start of treatment.

Results: At the time of writing, 24 pt were included (20 GIST, 4 other STS subtypes). In 2 GIST pts, the tumour was not FDG avid prior to treatment. Of the remaining 22 pts, CR_{PET} was seen in 10 pts and a clear PR_{PET} in 2 pts at day 8. All patients had major symptom relieve early after the start of treatment. Based on CT, objective tumour response (PR) was seen in 7/12 pts, however at later time points (3x at 4w, 3x at 8w, 1x at 16w). In the other 5 pts, categorised as SD according to RECIST criteria, treatment efficacy was presumed based on increased necrosis. SD_{PET} was found in 4 pts: 3 pts (1 non-GIST) still show SD on CT (FU 8m, 8w, 8w). In 1 pt, treatment was stopped after 8w because of increasing abdominal complaints and possible PD of the large abdominal mass on CT. PD_{PET} was seen in 6 pts (3 non-GIST) and a rapid increase in tumour-related symptoms was observed in 5 of them. CT confirmed PD in all 6 pts, 1 week to 1 month after the start of treatment.

Conclusion: PET seems to be a promising tool in the assessment of early tumour response. Treatment failure could accurately be predicted as soon as 1 week after the start of therapy. If response on PET also predicts survival remains to be answered.

113 ORAL

Second primary cancer after Ewing tumours - experience in 690 patients from a cooperative treatment study

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Purpose: Treatment of Ewing tumour involves high cumulative doses of drugs capable of inducing second primary malignancies. The second cancer risk in a large cohort of consistently treated patients was analysed.

Patients and Methods: 690 Ewing tumour patients between 1992 and 1999 received local therapy, and vincristine, actinomycin D, doxorubicin, ifosfamide and/or cyclophosphamide, randomised with or without etoposide. Second cancer incidences were estimated by competing risk analyses, standardised incidence ratios (SIR) were compiled in comparison to cancer registry data.

Results: 6/690 patients have developed second primary malignancies at a median observation time of 32 months: ALL/NHL, 2, MDS/AML, 2, liposarcoma, 1, squamous cell carcinoma, 1. In comparison to the general population, SIR were increased more than 20-fold. The cumulative second cancer risk 5 years after diagnosis of the Ewing tumour was 0.0093 for the total group. Etoposide, and additional phase II high-dose therapy increased the risk to 0.0118 and 0.0398 after five years, respectively.

Conclusion: The risk of second primary cancers observed was in the expected range for cancer survivors. High-dose therapy, and less markedly, etoposide may contribute to the overall second cancer risk.

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114 ORAL

Consistent evidence of activity of ecteinascidin (ET-743) in pretreated, advanced soft tissue sarcoma (ASTS): results from a pooled analysis of three pivotal phase II clinical trials (p2ct) and safety profile of a 24 h infusion schedule

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From 1/99 to 1/01, 194 patients (pts) with pretreated ASTS have been registered in three pivotal P2CT assessing efficacy of ET-743, 1.5 mg/m2, 24 h iv infusion q3w.

Main Endpoints: objective response (OR) rate and progression free rate at 6 months (PFR6m). Inactive agents have shown a progression rate of 82% within the first 6-8 w and active agents in ASTS induce a PFR6m of 18% (ASCO 2001; #1413).

Results: 127 pts have been evaluable for activity (median follow-up: 6 m). Median age: 51 yrs (18-76). M/F ratio 1:1.3. PS (ECOG) 0: 49.3%, 1: 50.7%. Histology: LeiomyoS: 41%; lipoS: 14%; synovialoS: 11%. Number of involved organs: 1: 44%; 2: 35%; >2: 19%. Prior treatment: neo/adjuvant: 28%; 1: 54%; 2: 26%; >2: 10%.; Median treatment duration: 3 cycles (cy)(1-20). Proportion of pts receiving 6 or more cy: 25%. The OR rate is 9.4% (CI95%: 5.0-15.9%). Minor responses have been noted in 11 pts (8.7%). OR have been observed in leiomyoS (6 pts), lipoS (3), synovialoS (2) and not specified sarcoma (1). The median time to OR has been 3 m and median duration of OR has not been reached (1.5±8+ m). Progression rate after 2 cy: 43%. The median time to progression and median overall survival are 2.8 m (2.0-3.6) and 10.2 m (8.7-11.7) respectively. The 1 yr survival and PFR6m are 40% and 27.2% respectively. Safety profile of ET-743 is based on available information from 163 out of the 379 pts treated with this schedule (518 cy) in any of the seven P2CT conducted in several tumors. The identification of baseline and drug-induced cholestasis as risk factors for severe toxicity (T) led to an amendment in October 1999 (ASCO 2000; #727). Main T per pt after the amendment (91 pts, 266 cy): grade (G) 4 neutropenia: 14%; G3-4 thrombopenia: 12%; G3-4 anemia: 18%; hyperbilirubinemia: G1-2: 9%, G3: 2%; G1-2 alkaline phosphatase: 46%; G3-4 ALAT: 40%; G2-3 nausea: 30%; G3-4 vomiting: 7%; G2-3 asthenia: 30%. Major SAEs: febrile neutropenia: 17/379 pts (4.5%); rhabdomyolysis: 6/379 pts (1.6%); toxic deaths: 4/379 pts (1.1%). Drug related mortality rate has been 1.6% (2/124 pts) and 0.8% (2/255 pts) before and after the amendment, respectively.

Conclusions: ET-743 is a valid therapeutic option in pretreated ASTS, inducing a prolonged tumor control in one fourth of pts. The identification of risk factors for severe T has improved its therapeutic index.

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Functional outcome after preoperative isolated limb perfusion with rhTNFalpha/Melphalan for high-grade extremity sarcoma

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Objective: To analyse long-term limb salvage rate and functional outcome in patients undergoing isolated limb perfusion (ILP) for locally advanced, high-grade soft tissue sarcoma of the extremities.

Patients and Methods: 55 pts. with high-grade sarcoma of the lower limb underwent ILP with TNF alpha plus melphalan followed by radical tumor resection including vessel graft and/or free myocutaneous flaps. patients. Mean tumor size was 9.6 ± 5.5 cm. No postoperative radiotherapy was administered in patients undergoing R0 resection. The functional outcome was analysed by using the rating scale of the Musculo-Skeletal Tumor Society (MSTS, best/maximum score 30 points) and physical disability was assessed with the Toronto Extremity Salvage Score (TESS, best/maximum score 100). Median follow-up is 33 months (4 - 69+ months).

Results: 51/55 patients underwent tumor resection and a clear margins (R0) could be achieved in 47/51 (92%). Primary limb salvage was possible in 44/51 pts (88%) and three of the seven amputations were minor (forefoot or ray). Local recurrence developed in four pts. (8%) and could be resected for cure in three of them, however, another patient required amputation.

The proportion of patients returning to work was 62.5%. Functional analysis by the MSTS score showed a median of 24 points (80% of the best possible score, range, 15 - 30). Functional disability analysis by TESS score resulted in 83,7 points (range, 46.5 -100). It could clearly be shown