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.

115 ORAL

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

that an improvement of function and adaptation to daily life routine took place during the second half year following completion of treatment.

Conclusions: Preoperative ILP combined with an aggressive surgical approach results in an excellent local control rate in high grade soft tissue sarcomas. Long-term limb salvage can be achieved in the overwhelming majority of our patients. Ranked by the patients themselves, functional results allow to maintain greater than 80% of preoperative routine activities.

Hematological malignancies

116 ORAL

Long-term follow-up of patients with newly diagnosed adult Acute Lymphoblastic Leukemia (ALL): A single institution experience of 378 consecutive patients over a 21-year period

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Purpose: Although the prospect of long-term leukemia-free survival (LFS) after treatment for adult ALL is widely accepted, few studies have reported long-term survival data. 378 ALL patients (pts), referred to our hospital from 1978 to 1999, were reviewed for long-term follow-up data.

Methods: The analysis included data on 351 pts treated by standard chemotherapy according to 11 different successive regimens.

Results: Complete remission (CR) was achieved in 299 pts (79%). Initial performance status, LDH level, immunophenotype, age, and risk group at diagnosis were of significant prognostic value for CR achievement. Median LFS was 14 months with a 3-year (y), a 5-y, and a 8-y LFS at 30%, 26%, and 24% respectively. LFS was better in T-lineage ALL than in B-lineage ALL ($p = 0.05$). Younger age was also a favorable prognostic factor for LFS ($p = 0.001$). Philadelphia-positive (Ph+) ALL displayed a poor outcome since median LFS was 7 months with only 13% of survival at 3 ys. Median overall survival (OS) of the entire cohort was 18 months with a 3-y, a 5-y, and a 8-y OS at 32%, 24%, and 22% respectively. Favorable prognostic factors for OS were younger age ($p < 0.0001$), and T-lineage ALL ($p = 0.001$). Among non T-lineage ALL, standard-risk ALL displayed a significant better outcome than high-risk ALL ($p = 0.0003$). All pts relapsing after 3 ys of CR were B- or non B non T-lineage ALL. Long-term survivors (LTS), defined as survival in CR $\geq$ 3 ys, represented 23% of evaluable pts. 83 pts remain alive in initial CR at >3 ys, while only 3 were LTS after a second CR. Regarding survival, a significant improvement was demonstrated in T-lineage ALL ($p = 0.03$). Furthermore, pts (aged less than 50 ys) transplanted while in first CR did significantly better than those receiving only chemotherapy as post-remission therapy ($p < 0.0001$). The 3-y OS, after allogeneic transplantation in first CR, was 74% in T-lineage ALL, while it was less than 50% in B-lineage ALL.

Conclusion: This single center study on a large cohort of unselected ALL pts reflects the degree to which ALL treatment remains unsuccessful in adults. Only T-lineage ALL outcome has improved over the ys. The results suggest a time (3 ys) at which it becomes reasonable to speak of potential cure, provided the pt is in CR.

117 ORAL

Treatment of patients with refractory, C-KIT positive, acute myeloid leukemia with SU5416, a novel receptor tyrosine kinase inhibitor

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In acute myeloid leukaemia (AML) increased microvessel densities have been detected on bone marrow histologies. Endothelial cell (EC) proliferation is driven by VEGF released by AML blasts. Stem cell factor (SCF) secreted by activated ECs or AML blasts may promote AML growth. SU5416 represents a small molecule inhibitor of phosphorylation of VEGF receptor-1 and -2 and of c-kit, the SCF receptor. This possible mechanism represented the rationale to initiate a phase II trial of SU5416 in patients with refractory AML.

Thirty-two patients (pts) with c-kit positive AML which was either refractory or occurred in patients older than 60yrs not judged medically fit enough for induction therapy, were treated twice weekly with 145 mg/m² SU5416 as a 60-minute infusion via a central venous device. From July 2000 to April 2001 15 female and 17 male patients with a median age of 68yrs (range 27-79) were enrolled. Treatment was generally well tolerated and toxicity was mild. Side effects included severe bone pain in 3 pts, liver failure with gastric hemorrhage and fatal shock (1 pt), grade IV pancreatitis (1 pt). Leukemia related side effects were: fatal thrombocytopenic hemorrhage (2pts), pneumonia/pyrexia/sepsis (6pts). 19 patients are evaluable for response: one patient with morphological remission (absence of blasts in peripheral blood and in bone marrow <5% without normalisation of peripheral blood thrombocytes and granulocytes), 7 pts with PR (reduction of blasts in blood and bone marrow by at least 50%) with a duration of 1-5 months, 11 pts were Non-responders after 4 weeks of therapy. 10 patients were non evaluable due to a treatment of less than two weeks caused by rapid disease progression after one infusion or serious adverse events due to underlying disease. 3 pts are too early to assess.

Treatment of c-kit positive AML with SU5416 represents a novel therapeutic approach. Administration of SU5416 was fairly well tolerated and toxicity was mild. Morphological and partial remissions were observed in a subgroup of patients. Future research is necessary to further identify the subgroup of AML patients where SU5416 shows activity.

118 ORAL

Troxatyl is effective in non-lymphoid blastic phase chronic myeloid leukemia (CML-BP)

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Troxatyl(TM) (troxacitabine) is the first dioxolane nucleoside with potent antitumor activity. In a Phase I study of Troxatyl in patients (pts) with refractory acute myeloid or lymphocytic leukemia, myelodysplastic syndromes or CML-BP, mucositis and hand-foot syndrome were DLTs (Giles et al, JCO 2001). The Phase II single agent dose was defined as 8 mg/m2/day daily for 5 days. Seventeen pts (10 F, 7 M; median age: 52 years, range: 23-80) with CMLBP have been treated at the recommended dose. Nine pts had failed prior therapy for CMLBP which included topotecan-based therapy - 5 pts, allogeneic SCT - 3 pts, 6 thioguanine - 1 pt, homoharringtonine - 2 pts, mitoxantrone/ara-C - 1 pt, STI571 - 6 pts, donor lymphocyte infusions - 1 pt, 2-CDA/cyclophosphamide/VP16 - 1 pt, hCVXD - 1 pt, clofarabine/decitabine - 1 pt, liposomal daunorubicin/ara-C - 1 pt, CVAD - 1 pt. Toxicities included Grade 2 skin rash - 5 pts, hand-foot syndrome Grade 2 - 4 pts, Grade 3 - 3 pts, Grade 2 mucositis - 1 pt, Grade 4 mucositis - 2 pts. Six pts (35%) have returned to a second chronic phase. The durations of 2nd chronic phase in these pts are 3 to 18 plus months. In a recent analysis of results in 162 pts following first salvage therapy for non-lymphoid CML-BP treated at MDACC between 1986 to 1997 (Sacchi et al, Cancer 1999), 36 pts (22%) had an objective response and the median overall survival was 22 weeks. The median survival in the Troxatyl-treated CML-BP patients is 52+ weeks at the present time ($p < 0.01$). Troxatyl is being studied as a single agent in a multicenter Phase II study of pts with CML-BP including STI571 (Glivec) failures. Initial data from this study will be presented.

119 ORAL

Zevalin radioimmunotherapy offers safe and effective therapy for relapsed or refractory, B cell non-Hodgkin's lymphoma (nhl)

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Zevalin consists of the anti-CD20 murine monoclonal antibody ibritumomab covalently bound to tiuxetan, which chelates 90Y for therapy. Zevalin therapy includes pretreatment with 2 doses of rituximab (250 mg/m2) 1 week apart to clear peripheral blood B cells and provide improved targeting. A total of 349 patients with relapsed or refractory low grade, follicular, or CD20+ transformed or intermediate grade B-cell NHL were treated with 90Y Zevalin on five clinical trials: a Phase I/II dose finding trial, a