from that in pts with normal serum sICAM1 and sVCAM1, 30%(3/10) and 33%(3/9), respectively. Following chemotherapy sICAM1 remained abnormal in 3/10 (30%) and sVCAM1 in 2/10 (20%) of the responders compared to 14/21 (67%, p=0.05) and 18/21 (86%, p<0.0001) respectively in non-responders. Median pre-treatment sICAM1 and sVCAM1 levels were not different in responders (259ng/ml and 1585ng/ml) compared to non-responders (237ng/ml and 1440ng/ml) respectively.

**Conclusions:** 1. Serum sICAM1 and sVCAM1levels are frequently abnormal in NSCLC patients. 2. Serum sICAM1 and sVCAM1 levels are related to tumour burden. 3. Neither sICAM1 nor sVCAM1 levels correlate with response to chemotherapy in advanced NSCLC.

### 569PD Immunohistochemic expression of multidrug resistance (MDR) proteins in non-small cell lung cancer (NSCLC).

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Frozen tumor samples of 95 patients with NSCLC (no prior treatment) were studied by immunohistochemistry for the expression of three MDR-related proteins: lung resistance protein (LRP), multidrug resistance protein 1 (MRP1) and P-glycoprotein (PGP) For each MDR protein, tumors were scored as positive if >10 % of tumor cells were stained The expression of these proteins was correlated with histology, grade and tumoral stage (UICC 1997) Histology subtypes included: 49 squamous carcinomas (SC), 38 adenocarcinomas (AC), 7 large cell carcinomas (LCC) and 1 mixed carcinoma

**Results:** 87% of tumors expressed at least one MDR protein (LCC 100%, SC 90% and AC 82%). The expression of MDR proteins was more frequent for LRP (68%) than for PGP (52%) or MRP1 (39%) (p<0.006) Co-expression of 3 MDR proteins was 18% (29% in SC). Among histological subtypes, LRP expression was more frequent in LCC (86%) and AC (79%) than in SC (59%) (LCC v SC; p=0.07). MRP expression was remarkably rarer in AC (5%) compared with SC (55%) and LCC (43%) (p<0.0001). No difference in PGP expression was seen among the various histologies: SC 53%, AC 53% and LCC 43% (p=0.7) There was no correlation between the expression of MDR proteins with grade and stage, except for lower LRP expression in stage I as compared with stage II to IV (p=0 04).

**Conclusions:** A high proportion (87%) of NSCLC express one or more of the MDR proteins, LRP, MRP1 and PGP. LRP is the most frequently expressed overall and, in particular, in AC and LCC as opposite to SC. MRP expression is remarkably infrequent in AC SC simultaneously expressed 3 proteins more often. There were no differences with respect to histologic grade and tumoral stage, except for LRP, which is less expressed in early stages.

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### 570PD Microsatellite alterations and TP53 mutations in plasma DNA of small cell lung cancer patients: Follow-up and prognostic significance.

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We undertook the present study to make a prospective investigation of the correlation between abnormal plasma DNA and the survival of patients diagnosed with SCLC Thirty-five patients with SCLC were studied. Genomic DNA, extracted from tumor tissue, normal blood cells and plasma, was used for molecular studies. Alterations, studied by two molecular methods, in polymorphic markers selected for their reported high rate of alterations in SCLC (ACTBP, UT762 and AR), and mutations in the TP53 gene were utilized to characterize tumor and plasma DNA We detected, LOH or shift, with microsatellite markers UT762, ACTBP2, AR(X), or mutation on TP53 gene in the plasma DNA of 25/35 patients (71%). The survival of patients with plasma DNA changes at the time of diagnosis (n=22; median survival: 57 weeks) with those of patients with no alterations in DNA (n=10; median: 46 weeks) revealed no statistically significant differences. The survival of patients with only microsatellite changes (n=12; median 28 weeks) or TP53 gene mutations (n=5, median. 59 weeks) and that of patients presenting both types of alterations concomitantly (n=8; median· 70 weeks), showed a statistically significant difference (p=0.02). In 17 patients of the 25 with abnormal plasma DNA (68%), a correlation was observed between the clinical behavior of their tumors and the presence of plasma DNA with alterations.

**Conclusion:** Microsatellite changes and TP53 mutations are presents in plasma DNA of SCLC patients, and these aberrations detected in plasma DNA may be used as a prognostic factor in SCLC patients.

## MELANOMA AND SARCOMA

### 571O Osteosarcoma in adults. An analysisss of 340 patients presenting in the third decade of life or later.

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**Objective:** Osteosarcoma is typically a disease of adolescents, but may occur at any age. While treatment strategy and prognosis are well defined for young patients, much less is known about affected adults. We therefore report the COSS experience for this patient cohort.

**Patients and methods:** All patients aged 20 years or older at diagnosis of a previously untreated high-grade osteosarcoma of a limb or the trunk (excl. head) registered into a neoadjuvant COSS-study before 7/98 were evaluated for patient and tumor related characteristics and outcome. Scheduled treatment included multiagent chemotherapy plus surgery of all tumor foci.

**Results:** 340 eligible patients were identified, 223 of whom presented in the 3rd, 63 in the 4th, 31 in the 5th, 17 in the 6th, and 6 in the 7 th decade of life. 51 primaries were located in the trunk, 289 in a limb. In 15 patients, OS represented a second cancer. After a median follow-up of 2.9 years, 225 patients were alive, 172 in 1 st remission, for actuarial overall and event-free survival rates of 62%/46% at 5 years and 53%/41% at 10 years. The corresponding values for 254 patients with localized extremity tumors were 72%/57% and 63%/51%. Tumor site (5 year survival axial 30%, limb 67%), primary metastases (yes 23%; no 68%), and histological response to preoperative chemotherapy (poor 60%; good 71%) correlated with outcome. Failure to achieve a complete surgical remission at any site was almost universally associated with tumor progression and death.

**Conclusion:** If treated according to the same principles, adult osteosarcoma patients can have a prognosis similar to that of adolescents with otherwise comparable tumor characteristics. The same prognostic factors seem to apply in both age groups

Supported by: Deutsche Krebshilfe

### 572O Results of a randomized, multicenter, phase III study of histamine dihydrochloride plus interleukin-2 (IL-2) versus IL-2 alone in patients (pts) with metastatic melanoma (MM).

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Immunotherapy with IL-2 produces <10% durable responses in pts with MM Monocytes/macrophages (MO) in the tumor microenvironment release free radicals and induce apoptosis in tumor-infiltrating lymphocytes. Histamine dihydrochloride (Maxamine®) inhibits the production of MO-induced free radicals, protects T cells and NK cells from MO-induced apoptosis, and restores reactivity to IL-2 Based on phase II studies in MM, a phase III, multi-center, randomized trial comparing IL-2 plus histamine to IL-2 in 305 pts with stage IV MM was conducted between 7/97 and 3/99 Eligibility criteria included age >18 years, no prior therapy with IL-2, Karnofsky score ≥ 70, and absence of brain metastases. Pts were randomized to IL-2 (9 MIU/$m^2$, bid, sc, days 1-2; wks 1, 3; and 2 MIU/$m^2$, bid, sc, days 1-5, wks 2, 4), administered to all pts for 4 wks of a 6 wk cycle, with or without histamine (1 0 mg, bid, sc, days 1-5, wks 1-4) Both drugs were self-administered on an out-patient basis for up to 8 cycles. The primary endpoint was overall survival (OS), prospectively applied to the intent-to-treat (ITT) and baseline liver metastasis populations, analyzed by the log-rank method. Secondary endpoints included time to progression (TTP), response rate, duration of response, and quality of life (QOL). Treatment with IL-2 and histamine significantly improved OS for pts with liver metastases (154 days to 282 days, p=0.004) and produced a trend to improved OS for the ITT population (p=0.125). TTP was also significantly improved in the ITT population (p=0.01). The incidence of serious adverse events was similar in the two treatment arms (34.4% (52/151) in the IL-2 plus histamine arm, and 38.8% (59/152) in the IL-2 only arm). The combination of histamine with IL-2 significantly improves survival over IL-2 alone for pts with MM who have liver metastases without significant toxicity or detriment to QOL.



  

## 573O Ecteinascidin-743 (ET-743) induces objective responses and disease control in patients with advanced non-osseous sarcomas: Results from phase II trials.

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ET-743 is a cytotoxic alkaloid derived from a marine organism which binds to the minor groove of DNA. Prior in vitro and phase I studies have documented potent cytotoxic activity of ET-743 in several tumors of mesenchymal origin. Phase II clinical trials have been conducted to assess the activity of ET-743 in patients (pts) with sarcomas who have had either (1) no prior chemotherapy (CT) or (2) 1-2 prior conventional chemotherapy regimens for advanced disease. Gastrointestinal stromal tumors (GIST) were entered into a separate trial. The phase II dose and schedule of ET-743 administration was 1500 mcg/m$^2$ by 24-hr continuous IV infusion on an outpatient basis, repeated every 3-4 weeks. Pts were restaged after every 2 cycles Accrual to all studies from 8/99 to 4/00: First-line = 17 pts; Prior CT = 30 pts, GIST = 14 pts. Tolerability of treatment has been excellent with dexamethasone pre-treatment for antiemetic prophylaxis. Other expected toxicities noted included fatigue, myelosuppression, and temporary and asymptomatic transaminitis. Uncomplicated fever with neutropenia occurred in only 2 of 61 pts (3%). Objective partial responses (PR) have been observed in 2 pts in the first-line study and 1 pt in the prior CT study. These PRs evolved over several cycles of treatment from stable disease or minor responses (MR). Additional MRs and stable disease are noted in 3 of 14 (21%) other evaluable pts in the first-line study and as have 7 of 21 evaluable pts (33%) with prior CT. These clinical benefits have been observed in liposarcomas, leiomyosarcomas, and synovial sarcoma. Stable disease has been observed in 1 of 14 evaluable pts with GIST. Pharmacokinetics of ET-743 have been rigorously assayed in all pts during the first cycle of therapy. ET-743 represents an active agent for the management of several histologic subtypes of sarcoma regardless of prior conventional chemotherapy.

## 574O Phase II study of ET-743 in advanced soft-tissue sarcoma (ASTS) in adult: A STBSG-EORTC trial.

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The objectives of this phase II study were to assess the activity and toxicity of ET-743 (Pharma Mar/Spain) administered at a dose of 1500 $\mu$g/m$^2$ as 24-hour continuous infusion every 3 weeks in pretreated patients (pts) with ASTS

**Results:** 47 pts have been included with a median age of 57 yrs (18-76 yrs), a median PS of 0 (0 to 1) and a median of 2 tumor sites (1-4). Three pts were ineligible and 16 pts are still on treatment. Despite exclusion of GIST (EORTC ongoing phase II study in chemotherapy-naive pts) 49% of pts had leiomyosarcoma. The median number of cy administered per pt is 3 (1-8). Toxicity (T): febrile neutropenia, G(grade) 3-4 neutropenia and thrombocytopenia were observed in 11, 38 and 21% of pts respectively. Reversible transient elevation of transaminases occurred in the majority of cy (G3-4 in 17 pts). There were 3 toxicity-related deaths, 2 after the 2nd cy due to neutropenic fever, renal insufficiency and liver dysfunction, and 1 after the 1st cy due to neutropenic sepsis Renal T occurred in 3 other pts in the first 2 cy. There was no alopecia and no severe digestive T. The severe T were highly correlated with 1) an abnormal baseline alkaline phosphatase (ALP) and 2) a rise of ALP and/or bilirubin (bil) between cy. To date, 6 pts are not evaluable for response and evaluation is awaited in 9. In 29 evaluable pts we observed 3 PR, 3 not confirmed PR, 2 prolonged MR, 9 NC and 12 PD. After protocol amendment requiring normal ALP at inclusion and ET-743 dose reductions (1200 $\mu$g/m$^2$) in case of an intercycle-rise in bil/ALP equal to or exceeding G1, T has been manageable. ET-743 seems to be an active drug in ASTS and deserves further development.

## 575O Comparison of peer-review (PR) and independent radiologist (IR) review of claimed responders in a phase II study treating advanced soft tissue sarcoma of the adult with high dose ifosfamide. An EORTC study.

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Response rates (RR) are used to indicate potential activity of new anti-cancer agents and PR or IR increases objectivity. If positive, larger studies using traditional end points further evaluate clinical benefit. The main aim of this phase II study, undertaken by the Soft Tissue and Bone Sarcoma Group (STBSG) of the EORTC was to determine efficacy of high dose ifosfamide, dose 12 mg/m$^2$ given as a continuous infusion over 3d q28d with Mesna in advanced soft tissue sarcoma of the adult by RR This facet of the study was to determine whether PR was suitable for the review process or is an IR should be incorporated. At least 1 bidimensionally measurable lesion of at least 2cm in the lungs or 2 5cm in the abdominal viscera or other sites on chest radiograph or cumputed tomography was required and WHO response criteria were used. PR of claimed responders was by 2 members of the STBSG and agreement was required to confirm the response, otherwise the worst response by PR was assigned. An IR reviewed these cases, though was blinded to the results of the PR and vice versa. 22 patients (pts) were claimed as response and 16 and 17 were confirmed by IR and PR respectively and 6 (27%) and 5 (23%) were rejected for not fulfilling the criteria for response or were not evaluable. 3 pts were later found to have progressive disease by IR and 1 by PR. Response was only different in 1 pt indicating good agreement between the IR and PR. This indicates that PR is satisfactory in this tumour type for RR, though an IR may be incorporated into the review process if time to progression is a major end point.

## 576P Prognostic factors and survival in adult patients with small round cell tumors.

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The primary objective of this study is to review the clinical characteristics of 25 adult patients treated with small round cell tumors. In addition, survival and prognostic factors influencing the outcome with multimodality treatment are evaluated.

There were 19 males (76%) and 6 females (24%). The median age was 26 years (15-56) In 9 patients (36%) the tumor was located at an extremity, while 16 patients (64%) had central localisations Tumor size was larger than 10 cm. in 7 patients (29.2%). Six patients (24%) presented with metastatic disease. Twelve patients (48%) received radiotherapy. Tumors were resected with marginal margins in 2 patients (13.3%); while 2 patients had a radical resection and 12 (80%) had wide resections. All patients were given a median of 4 cycles of multiagent chemotherapy (1-14 cycles).

With preoperative chemotherapy, complete regression (CR) of the tumor was achieved in 6 patients (25%). In 4 patients (16.7%) a partial response was obtained. After the completion of multimodality treatment, 12 patients (48%) had a CR. Progression-free (PFS) and overall survival (OS) for the entire group was 25.0±10.8 % at 1 year and 30.5±15.5% at 3 years, respectively Non-metastatic disease, wide and radical resection, and presence of CR to multimodality treatment were associated with a significantly longer PFS and OS by univariate analysis. By multivariate analysis, CR to multimodality treatment was the only independent predictive factor for a longer OS (p: 0.0036, RR: 23.6, 95% CI: 2.8;198.7) and metastatic presentation was the only independent factor predictive for a shorter PFS (p:0.017, RR. 15, 95% CI: 1.6;141.2).

Large-scale, multicenter studies are required for a better evaluation of the adult population with small round cell tumors.

## 577P Differences in haemostatic disorders in patients with metastatic malignant melanoma and patients with mestastic testis carcinoma.

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Haemostatic disorders are frequent in cancer patients (pts) being detectable in about 50% of pts with localized tumor and in more then 90% pts with metastatic disease. There is a association between the type of malignant disease and the type grade of haemostatic disorders. In this study pts with disseminated malignant melanoma (dMM) and pts with disseminated testis carcinoma (dTC) were tested with the aim to determine type and intensity of haemostatic disorders in those diseases. Same parameters were determined in the group of healthy donors. Results revealed significant increase in fibrinogen



 

concentration in both groups of pts. In pts with dMM, there is a significant discrepancy between fibrinogen concentration determined by immunological (rid) and functional methods (there is an unusual concentration of biologically inactive molecules). In pts with dMM, plasminogen concentration, tested by functional method (chromogenic method - CHR), is significantly increased; fibrin/fibrinogen degradation products (latex technique) were detected in 37.3% of cases, implying that there is an activation of the fibrinolytic process. In both investigated groups complexes thrombin-antithrombin III (TAT) were significantly increased (dTC, $\bar{x}$=15,3 $\mu$g/l, dMM, $\bar{x}$=43,6 $\mu$g/l, healthy donors, $\bar{x}$=3,4 $\mu$g/l) implying the activation of coagulation system, particularly in pts with dMM. $C_1$ inhibitor concentration was significantly increased in both groups of pts (dTC $\bar{x}$=0,361 $\mu$g/l dMM $\bar{x}$=0,436 $\mu$g/l, healthy donors $\bar{x}$=0,228 $\mu$g/l); this protein behaves as a parameter of biological evolution of the disease. Other investigated parameters: antithrombin III, factor VIII, $\alpha_2$ macroglobulin, $\alpha_2$ antiplasmin were not significantly changed if compared with the group. Our results reveal that there is a pathological activation of blood coagulation, in both group of pts, particularly in those with dMM. In this group pathological haemostatic activation is significantly increased and it is followed by the activation of fibrinolytic process.

## 578P Human herpes virus type 8 (HHV8) in non-HIV related Kaposi's sarcoma in Egyptian patients.

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Recently, novel DNA sequences, termed Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus type 8 (HHV8), have been detected in the vast majority of tissue specimens of AIDS associated KS. Some studies succeeded to detect the virus in other types of KS (classic, endemic African, iatrogenic). This led to the hypothesis that this new herpesvirus has a key role in the pathogenesis of KS. Using the polymerase chain reaction (PCR), we studied 33 Egyptian non-AIDS (classic) KS patients as well as 15 healthy age and sex matched controls, for the presence of HHV 8 DNA Biopsies from lesional skin were examined in all patients. Biopsies from normal perilesional skin and serum samples were taken from only 10 cases and from all controls. HHV8 DNA sequences were detected in lesional skin of 84.8% (28/33) of cases, 80% (8/10) of serum and 70% (7/10) of perilesional skin, compared to negative skin and serum samples from all controls All our patients were serologically negative for AIDS, had normal blood counts, normal CD4/CD8 ratio and had no history of receiving immunosuppressive drugs. These results support that HHV8 is implicated in the pathogenesis of KS irrespective to the state of immune competence of the patients as well as the geographical regions.

## 579P Synovial sarcomas, a single center retrospective analysis.

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**Aim:** Evaluation of prognostic factors and the efficacy of the treatment in synovial sarcomas.

**Material and methods:** 24 patients (pts) with the diagnosis of synovial sarcoma, admitted at the IPO Porto from 1974 to 1999, were retrospectively evaluated according to location, dimensions, histologic differentiation, necrosis, and type of treatment

**Results:** There were 15 females and 9 males with a median age of 30 5 (min 8- max 78) years. The location of the tumour was: upper limbs 3 (12.5%), lower limbs 18 (75%), trunk 2 (8.3%) and neck 1 (4.2%.). Twelve had $\leq$ 5cm (50%),8 (33 3%) had >5cm and 4 (16.7%) were undetermined. Two patients with grade I(8.3%), 1 with grade II (4.2%) 8 with grade III (33.3%) and 13 undetermined (54.2%). Necrosis was present in 8 patients, absent in 1 and undetermined in 15 patients. The clinical staging (AJCC) was: stage I: 2 (8.3%), stage II: 1 (4.2%) stage III: 6 (25.0%), stage IV: 2 (8.3%) and undetermined in 13 (54.2%) pts.

Chemotherapy adriamicin based was the primary treatment in 11 pts (ADR+DTIC in 4 pts, CYVADIC in 4 pts, MAID in 1 pt and VAC in 2 pts); radiotherapy was the primary treatment in 15 pts. All but two pts were submitted to surgery, 19 with negative surgical margins and 3 with positive margins. Metastases occurred in 13 pts (54.2%),lungs 7 (29.2%), liver 1 (4.2%), local recurrence 2 (8.3%) and multiple 1 (4.2%).

**Conclusions:** Of all the variables evaluated only the clinical dimension attained statistical significance regarding disease free and overall survival (p=0,05).

## 580P Method of detection for local recurrence of extremity soft tissue sarcoma (STS): Implication for surveillance.

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The follow-up strategies for detection of STS local recurrence after definitive surgical resection of the primary tumor needs to be determined. The aim of our study was to determine the method of relapse detection. We reviewed the medical records of 36 locally relapsing patients. 23 primary lower and 13 upper extremity STS, treated between April 1979 and September 1996. The surveillance program commonly included a physical examination every 3 months within 2 years, and then every 6 months, computed tomography (CT) scan and/or magnetic resonance imaging (MRI) were routinely performed at the time of the clinical examination. All patients developed local recurrence disease with a 10 months of median disease free interval (DFI) (range· 2-168). There were 19 male and 17 female No patients had a local progression within the first 2 months following the completion of initial treatment Detection on the basis of symptoms and clinical examination was obtained in 16 patients. An abnormal CT scan or/and MRI detected local recurrence in 11 patients. The median DFI was shorter for patients who had a local relapse detected by CT scan than for those detected by symptoms: 7 months (range 3-168) versus 15 months (range: 3-72) respectively (Log-rank: p=0.05, Wilcoxon: p=0,007). The median overall survival from local recurrence were similar for both group of patients: 15 months (range: 1-129).

**Conclusion:** at this time, it seems reasonable to perform routinely CT scan/MRI for the surveillance of extremity STS.

## 581P Autoantibody prevelance in high-risk melanoma patients treated with adjuvant high-dose interferon $\alpha$-2a.

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The induction of increased circulating levels of antithyroid and antiphospholipid antibodies has been reported in patients with disseminated metastatic melanoma treated with immunotherapy As high-dose interferon with intravenous induction phase is widely adopted for stage IIB and III patients and will be investigated in stage IIA patients we prospectively evaluated the induction of antithyroid, antinuclear and anticardiolipin antibodies in high-risk melanoma patients (T4-N0 and all N+) receiving 15MU/m$^2$/d (iv) 5 days per week for 4 weeks. Forty-eight patients (median age 52 years, range 27-72 years, 23 male and 25 female) with histologically proven stage IIB or stage III primary cutaneous melanoma after appropriate surgery were included in our study. Blood samples were obtained prior to induction therapy and at the end of four weeks prior to consolidation therapy. For the quantitative measurement of antimicrosomal, antithyroglobulin, antinuclear and anticardiolipin antibodies an immunoenzymometric assay was used. Prior to treatment 6 patients had antinuclear antibodies, 2 patients had antithyroid antibodies, 3 patients had IgG anticardiolipin antibodies and 4 patients had IgM anticardiolipin antibodies After completion of one month induction treatment an induction of antinuclear antibodies was observed in 2 patients, of IgM anticardiolipin antibodies in 6 patients No induction of antithyroid antibodies was seen.

**Conclusion:** In this study the low-incidence of therapy induced autoantibodies suggests that no routine monitoring should be performed in the large population of stage IIA melanoma patients receiving one month immunotherapy with interferon $\alpha$-2a

## 582P Interferon $\alpha$ (IFN$\alpha$), interleukin-2 (IL-2) and cisplatin (CDDP) in metastatic melanoma (MM) and advanced soft tissue sarcoma (ASTS).

Hector G Botto, Marta L. Otegui, Marcelo E. Botto, Ruben Delia, Maria Rios. *FOI, Buenos Aires, Argentina*

**Purpose:** Experimental and clinical trials have shown therapeutic possibilities with a combination of IFNa, IL-2 and chemotherapy in renal cell carcinoma and melanoma. This study was performed to evaluate feasibility, efficacy and toxicity of IFNa, IL-2 and CDDP combination in recurrent metastatic melanoma and locally advanced soft tissue sarcoma.

**Methods:** 21 patients (pts), median age 43 (31-65), M 11, F 10, PS 0-1: 14 pts, 2: 7pts, distribution: 11 pts MM and 10 pts ASTS. All pts had progressive desease after previous chemotherapy regimens. Treatment consists of CDDP 50 mg/m$^2$, days 1-2, IFNa 5 MU sc days 3-8, IL-2 9 MU sc days 10-15 every 21 days in MM and CDDP 50mg/m$^2$ days 1-2, IFNa 5 MU intralesional days 3-8, IL-2 9 MU sc days 10-15 every 21 days in ASTS, until progression or toxicity.

**Results:** RR (CR + PR): MM 18%, ASTS 30%. SD: MM 36%, ASTS 40%. PD: MM 45%, ASTS 30%; progression-free survival: median 3 months (2-16) in MM and 12 months (3-41) in ASTS.



  

Toxicity: Neutropenia Gr.2/3, thrombocytopenia Gr.2/3. Other manifestations: nausea, vomiting, mucositis, diarrhea, fatigue, fever.

**Conclusion:** These results suggest that combination of IFNa sc and intralesional, IL-2 sc and CDDP, in pretreated pts with recurrent MM and pretreated pts with locally ASTS, were well tolerated, had antitumoral response and clinical benefits

## 583P Phase II trial with antisense oligonucleotide ISIS 3521/CGP 64128A in melanoma patients: A report from the EORTC/ECSG.

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ISIS 3521 is a phoshorothioate antisense oligonucleotide which hybridizes to the 3'-untranslated region of human PKC-α mRNA and inhibits PKC-α expression through RNase H-mediated cleavage of hybridized PKC-α mRNA. In vitro and in vivo studies suggest that ISIS 3521 may be useful for the treatment of patients (pts) with cancer. The ECSG performed a trial to determine the efficacy and safety of ISIS 3521 in melanoma pts. Pts had at least one measurable lesion, adequate bone marrow, liver, renal function, normal PT/APTT and did not receive prior chemotherapy (except adjuvant or local) and no prior radio- or immunotherapy within 4 weeks In total 27 pts were included (male/female 13/14) with a median age of 51 years (32-72), and a median WHO PS 0 (0-2). Pts were treated with 2 mg/kg/day ISIS 3521 x 21 days q 28 administered as continuous IV infusion through a central venous line A total of 55 cycles were administered to 26 pts, median of 2 cycles per pt (1-8) The majority of pts (22) received 1 or 2 cycles CTC grade (G)1-2 side effects occurring most frequently were nausea (10 pts), vomiting (4), fatigue (10), myalagia (2), increased liver enzymes (2), headache (3), fever in absence of infection (7). G3 side effects included anorexia (1 pt) and fatigue (2). Over 54 cycles analyzed for hematological abnormalities, anemia G1-2 was observed in 35 cycles Thrombocytopenia G1-2 was observed in 24 cycles, while in 5 cycles (4 pts) G1 APTT increase was reported. A moderate rectal bleeding was the single possible drug related serious adverse event No drug related death was reported Of 23 pts evaluable for tumor response, 21 had progressive disease while in 2 pts stable disease was reported.

**Conclusion:** ISIS 3521 administered in this regimen was fairly well tolerated. No tumor responses were obtained with ISIS 3521 as single agent at this dose and schedule. Further studies should investigate if combination treatment with ISIS 3521 is clinically relevant.

## 584P Ewing's sarcoma and peripheral primitive neuroectodermal tumors (pPNETs): Results of combined modality treatment in our experience.

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We reviewed the clinical features, treatment, and outcome of 20 patients (pts) with Ewing's sarcoma and pPNETs treated at our institution. Median age was 22 years (range: 15-57). Primary tumor sites were: proximal extremities 7, distal extremities 5, trunk 6, extraosseous 2 Fourteen pts (70%) had nonmetastatic tumor and 6 pts (30%) had metastatic disease at presentation. Most of the localized pts (10/14) received neoadjuvant therapy that consisted of VAC regimen (cyclophosphamide, vincristine, and doxorubicin) in 4/10 pts, VAC/EI (etoposide, ifosfamide)in 2/10 pts, VAC/VAI (vincristine, dactinomycin, and ifosfamide) in 3/10 pts and HDI-E (high dose ifosfamide plus sequential epirubicin) in 1/10 pt initially diagnosed as extraosseous chondrosarcoma. All but one pts responded to chemotherapy (CT) and underwent local treatment with surgery (5/10) and/or radiotherapy (RT) (7/10). Treatment plan was completed by adjuvant CT (median cycles/pt: 4, range: 2-9). Surgery was the primary treatment in 4/14 pts with localized disease followed by CT and/or RT At a median follow-up time of 63 months (range: 3+ - 142+) 11/14 pts (80%) are alive without evidence of disease. Two pts with primary tumor site at femur, greater than 8 cm in size, relapsed after 13 and 44 months, respectively, and one pt who presented with localized Ewing's sarcoma of pelvis did not respond to treatment and died within 18 months due to distant relapses All six pts with metastatic disease received combination CT. The median number of cycles/pt was 6 (range: 2-6). Four pts achieved a partial response one pt that underwent RT and surgery after CT is in remission 12+ months from diagnosis, one pt is not assessable and two pts relapsed. Based on this limited experience we conclude that long-term control can be achieved in pts with localized disease. Disease extension predicts worse outcome and strategies of treatment intensification for these pts should be investigated.

## 585P Is it safe to substitute oral for intravenous Mesna? A case control study.

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There is limited evidence that oral preparations (p o.) of Mesna are as effective as intravenous (i.v.) Mesna in preventing uro-epithelial toxicity caused by ifosfamide (>2 g/m$^2$). There is no guidance on monitoring of patients taking p.o. Mesna. This study investigated the safety and tolerability of p.o. Mesna to replace i v Mesna after a final dose of ifosfamide.

**Patient and Methods:** Twenty-four patients with sarcomas receiving inpatient ifosfamide chemotherapy (3 g/m$^2$/day for 2 or 3 days) were studied. Patients acted as their own controls. In group A, patients received i.v. Mesna (3 g/m$^2$), for 12 hours after last dose of ifosfamide. Urine was monitored for haematuria, by dipstick of all samples and microscopy of two samples In group B, an i v. bolus of Mesna (600 mg/m$^2$) and tablets of Uromitexan (Asta-Medica) were given, in accord with data sheet, 2 and 6 hours later (1200 mg/m$^2$). Toxicity, complications and patients acceptability were noted.

**Results:** Eight patients (33%) in group A and 10 (42%) in group B had grade 1 nausea and vomiting. Ten patients (42%) in group A and 9 (37%) in group B had grade 2 toxicity. Two patients (8%) in group B required the first dose to be represcribed. Seventeen (71%) patients on group A and 15 (62 5%) on arm B required antiemetics in addition to those routinely prescribed There were no positive dipsticks in group A, but the first of two samples in one patient showed 128rbc/ml (grade 4) haematuria when assessed by microscopy. In group B no haematuria was seen. Eight of 48 samples were unassessable One patient had symptoms of cystitis, but no haematuria and responded to antibiotics There were no recorded adverse effects of oral treatment. Twenty two patients (92%) preferred oral therapy. It was unacceptable to the 2 patients in whom it induced vomiting Cost saving were limited to those of earlier discharge.

**Conclusion:** An oral preparation of Mesna was not obviously less effective than i.v. administration in preventing ifosfamide induced urotoxicity. It was generally well tolerated, and preferred by most patients. Further studies are required into the need for urine monitoring during p.o. Mesna therapy.

## 586P Results of a T10-derived protocol based on preoperative high-dose methotrexate with individual dose adjustment in the treatment of primitive osteosarcoma.

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Adolescents and adults with primitive osteosarcoma were treated with a T10-derived protocol in a single center between 1987-1997 Preoperative chemotherapy consisted of 4 weekly cycles of high-dose methotrexate (HDMTX) with individual dose-adjustment. After surgery, patients classified as good responders (grade III-IV necrosis) received an adjuvant chemotherapy based on HDMTX, theprubicin (THP) and BCD, whereas poor responders (grade I-II necrosis) received a salvage chemotherapy based on cisplatin, THP, ifosfamide +/- etoposide. Forty-two patients with osteosarcoma (35 patients with localized disease and 7 with metastatic disease) were treated Their median age was 24 years (15-53). Primary tumor sites included extremities (90.4%), axial bones (7.2%) and head and neck (2.4%). Limb salvage was performed in 72 5% of cases. A good histologic response rate was obtained at 11 2%. With a median follow-up of 50 months (6-134), the 5-year overall survival (OS) rate was 65 7% for the entire group For the 35 patients with localized disease, the 5-year OS and event-free survival (EFS) rates were 75 8% and 64.6% respectively. The difference in EFS and OS rates at five years between good and poor responders was not significant In multivariate analysis, tumor size, dose intensity and preoperative MTX dose intensity were independent prognostic factors for OS (P=0.004, 0.04, 0.007 respectively). With this protocol, although the good histologic response rate obtained was low, salvage chemotherapy was successful for poor responder patients yielding similar EFS and OS rates as those of good-responder patients. The EFS and OS rates obtained were superimposable to those reported in the most recent studies.

## 587P A pilot study of dose-intensive multiagent chemotherapy for extremity osteosarcoma with pulmonary metastases.

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**Aim:** To assess the feasibility, toxicity and response to short course, multiagent chemotherapy culminating in peripheral stem cell supported high-dose chemotherapy.

**Patients and methods:** Between May 1995 and April 1999, 14 patients (12 male/2 female) were enrolled. Median age 17 (range 8-32), Location: femur (9), tibia (2), humerus (2), fibula (1) Proximal: 7, distal 7 Chemotherapy consisted of five blocks given consecutively: Block 1: cisplatin 100 mg/m$^2$,



 

doxorubicin 75 mg/m$^2$ q 14 days x 2. Block 2 (x1). cisplatin 50 mg/m$^2$, ifosfamide 4 gr/m$^2$, and etoposide 500 mg/m$^2$ (Stem Cell Harvest post Block 2). Block 3 ifosfamide 18 gr/m$^2$ q 21 days x 2. Block 4: methotrexate 12 g/m$^2$ q 7-10 days x 3. Block 5 (administered around week 21): carboplatin AUC8 and etoposide 400 mg/m$^2$ on days -8, -6, and -4, cyclophosphamide 60 mg/kg on days -6 and -4. On day 0 patients underwent reinfusion of their harvested stem cells.

Local management included a) limb salvage surgery: 13/14 patients, b) amputation: 1/14. Seven patients (50%) underwent pulmonary metastasectomy.

**Results:** Average number of cycles administered per patient: Block 1 (2), Block 2 (1), Block 3 (2), Block 4 (2.5), Block 5 (0.7). No. of cycles administered at full dose: Block 1 (97%), Block 2 (100%), Block 3 (70%), Block 4 (83%). Number of cycles delayed > 1 week: Block 1 (11/27), Block 2 (3/14), Block 3 (6/26), Block 4 (1/22). Cumulative grade 3/4 toxicity per cycle (excluding Block 5): WBC: 42%, Hb: 15%, Plts: 23%, infection: 28%, stomatitis: 8%, nausea: 7%. Encephalopathy: 3/14 patients. Treatment related mortality occurred in one patient. Responses: CR: 0/14, PR: 8/14 (58%), mR: 2/14 (14%), SD: 3/14(21%), PD: 1/14(7%). 2-year survival: 50%, Median survival: 21 months (7-55).

**Conclusion:** Dose intensive multiagent chemotherapy is feasible in this group of patients with adverse features, with acceptable toxicity and satisfactory 2-yr survival rates.

## 588P First line chemotherapy with ifosfamide (IFO)-doxorubicine (DOX) in unresectable or metastatic soft tissue sarcomas (STS).

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IFO and DOX in monotherapy are the most active drugs against STS. Their use in polychemotherapy improves response rates in metastatic patients (pts) Activity and safety of the combination of these drugs in pts with unresectable or metastatic STS are presented.

**Methods:** Elegibility: histological diagnosis of STS, normal haematological count, adequate visceral function and PS 0-2. Treatment IFO 2.5 g/m$^2$ d 1-2, DOX 70 mg/m$^2$ d 1 /21 d, until unacceptable toxicity, progressive disease or maximal accumulative dose of DOX (490 mg/m$^2$). Dose was reduced by 20% if grade 3-4 toxicity.

**Results:** from February 1997 to February 2000, 25 pts. were treated, 20 male. Mean age: 53 2 year-old (28-76). Pathology: malignant fibrous histiocytomas 7, leiomyosarcomas 3, synovial sarcomas 2, liposarcomas 2, epithelioid sarcomas 2, stromal digestive sarcomas 3, other types 6. High or intermediate grade 16 (64%), low grade 4 (16%), unknown: 5 (20%). Sites of disease local 12, lung 12, nodal 6, pleural 4, liver 2, bone 2 More than one metastatic site: 9 cases. One hundred and eighteen have been administered. Mean: 4.7 cycles/patient (pt) (range 1-8). Toxicity grade 3/4: anaemia 3/0 episodes (ep), neutropenia 4/4 ep, asthenia 4/0 ep, emesis 3/0, mucositis 3/0 ep. Total grade 3-4: 22 (19%) ep. Dose reduction in 7 (28%) pts. Responses (WHO) Evaluable pts 23 (1 early death, 1 too early) CR 2/23 (9%), PR 4/23 (17%), SD 8/23 (35%), PD 9/23 (39%) Overall response rate (CR+PR) 6/23 (26%, 95% CI ±17 8%).Tumoral growth control (CR+PR+SD) 14/23 (61%, 95% CI ±19.9%). Median overall survival: 9 months (range 1-24). Only 35% pts survived more than one year.

**Conclusions:** The scheduled treatment is both feasible and active, with tolerable toxicity, but median survival is in the range of other published studies. New drugs or combinations are needed to improve results for these diseases.

## 589P Response to high dose ifosfamide (IFO) in sarcoma bearing patients (pts) previously treated with standard doses of ifosfamide.

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HIFO is a regimen that has been administered at our center since 1990. Feasibility and toxicity have been already reported. (ASCO '98 #2125). In the present study we communicate the results of HIFO in 29 pts previously treated with anthracyclines and ifosfamide.

M&M: Since 1994 73 cycles of HIFO were performed in 29 pts with diagnosis of advanced sarcoma. Median age was 32.9 y (16-60), ECOG performance status 0: 3, 1: 15, 2: 9, 3. 2. Diagnosis: osteosarcoma (8), Ewing related tumors (6), malignant fibrous histiocytoma (3), leiomyosarcoma (3), synovial sarcoma (2), others (7). All of them have been previously trated with anthracycline and ifosfamide containing regimens. Doses of ifosfamide ranged between 7-9 g/m$^2$ and both drugs have been used in the neoadjuvant, adjuvant or palliative setting, either sequentially or in combination.

Treatment: Ifosfamide (3h infusion) 3.2 g/m$^2$ d1, 1 8 g/m$^2$ d2-7 with Mesna 20% of the daily dose of ifosfamide hour 0, 4 and 8 each 21-28 days.

**Results:** Four pts were not evaluable for response as they received only one cycle because of significant toxicity in a second or third line setting. Response: CR:2 pt, 12m and +4m (one pathologic), PR: 5 pts, 7, 7, 5, 4 and +2m. ORR: 7/25 (28%), all responses were evident at the end of second cycle. Additionally one pt had a PR, but progressed in CNS. Toxicity per cycle was assessed with the US-NCI scale. GIII-IV neutropenia: 8 (5 plus fever); GIII-IV thrombocytopenia: 3; GIII-IV anemia: 1. One hematuna GII and one GIII. Renal toxicity was mild perhaps related to alcalinization: creatinine GII: 1 cycle and one had hyponatremia due to tubular damage One pt had neurocortical toxicity GII. There were no toxicity-related deaths.

**Conclusion:** HIFO is a useful regimen, even in ifosfamide-pretreated patients and responses are evident with two cycles.

## 590P Phase II trial of paclitaxel-epirubicin in recurrent soft tissue sarcoma (STS).

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Between June 1998 and January 2000, 27 patients with recurrent histologically confirmed STS entered into a multicenter study to determine the efficacy and safety of the association paclitaxel-epirubicin Standard eligibility criteria applied measurable disease, normal blood count, normal cardiac function, signed informed consent. Paclitaxel was given as a 3 hours infusion at a dose of 200 mg/m$^2$, epirubicin was administered as a short infusion at a dose of 75 mg/m$^2$. Chemotherapy courses were administered every 21 days A total of 74 cycles were given to date. All patients were assessable for toxicity and response. Patients characteristics included: 14 females and 13 males, median age of 52 years (range 20-68) Initial localization of primary tumors were: extremity (16), abdominal (3), retroperitoneal (4), uterine (2), breast (1), cardiac (1). The most common histologic types were: leiomoysarcoma (6), synovialosarcoma (3), angiosarcoma (3), liposarcoma (2). Locally recurrent and distant metastasis disease occurred in 12 and 20 patients, respectively. The median disease free interval was 14 months (range 2-152). Fourteen patients had previously received a first line anthracycline based chemotherapy for recurrent disease, and 3 patients were treated with two line chemotherapy. Main hematologic toxicities were grade 3-4 neutropenia (70%), grade 3 anemia (3.7%), grade 3 thrombocytopenia (7.4%). Febrile neutropenia occurred in 5 patients (18.5%), one death was due to drug related neutropenic sepsis. Severe non hematologic toxicities rarely occurred: grade 2-3 alopecia (85.2%), grade 1-2 nausea/vomiting (48.2%), grade 1-2 paresthesia (25.9%), grade 1-2 mucositis (25.9%), no cardiac toxicity was observed. Two patients had a partial response (7.4%; 95% confidence interval: 2 6-12.2%), with a median response duration limited to 3 and 5 months Six patients had a stable disease (22.2%), and 19 patients had a progressive disease (70.5%). The median overall survival from study inclusion was 8 months (range: 1-15 months).

**Conclusion:** from these data the association of paclitaxel to epirubicin seems to have no significant activity in recurrent STS.

## 591P Low dose interferon-$\alpha$ + tamoxifen in the treatment of recurred melanoma patients after adjuvant therapy: The experience of Melanoma Cooperative Group of Naples.

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**Background:** Little is known about treatment of melanoma patients who recur during adjuvant treatment. Our previous study about utilizing IFN increased dose after recurrences during or after adjuvant therapy with low dose IFN (LD-IFN) showed negative results [ECCO 10: Eur J Cancer 1999; 35: S370. (abstr.)]. The aim of the present study was to verify if low doses tamoxifen (TAM) are able to restore melanoma sensitivity to IFN.

**Patients and Methods:** From January 1999 to March 2000 21 consecutive CM patients (12 males and 9 females; median age 59 yrs, range 31-75 yrs) with local, in transit or lymph node recurrences during adjuvant therapy with LD-IFN (IFN$\alpha$-2b 3 MU/d TIW SC), or ID-IFN (IFN$\alpha$-2b 10 MU/d TIW SC), or vaccine therapy (BCG+C-VAX or BCG+placebo; Morton et al. Oncology 1999; 13 1561-74), who had no evidence of disease (NED) after surgical treatment of metastasis, were enrolled for a second line therapy with IFN$\alpha$-2b 3 MU/d TIW SC + TAM 20 mg p.o. daily; treatment was planned for 1 year

**Results:** At present, 2 pts have completed 1 year of therapy (median 9 months, range 2-12 mts); however, so far, only 1 pts has relapse after 2 months of therapy. Treatment is well-tolerated and has never been suspended or reduced for toxicity. Main toxicity was flu-like syndrome related to IFN administration, and flushing and dizziness related to TAM.

Discussion: Preliminary results show that, in spite of the short follow up and the small sample size, TAM could potentate IFN activity. In fact, in our previous study, relapse occurred mainly within early months of treatment. Disease



  

progression could determinate a switch of melanoma cells malignancies and, thus, less differentiated clones of melanoma cells could become resistant to IFN action TAM could act increasing sensitivity of IFN resistant clones of melanoma cells.

## 592P DTIC + carboplatin + IFNα2a in metastatic melanoma: Renal Cancer and Melanoma Spanish Group.

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From May 97 to March 2000, 30 pts with metastatic melanoma without prior treatment received chemotherapy according the schedule DTIC 500 mg/m$^2$ day 1, carboplatin AUC-6 (reduction 25% in pts >60 years old), both given every 28 days IV and IFNα6MU/m$^2$ SC 3 days a week.

Patients characteristics: Sex 14 males, 16 females ECOG 0-2 age (median 50,86) (18-72), 16 pts (53.3%) have more than one metastatic site of disease.

Eligibility criteria included: Stage IV melanoma without previous treatment and normal major organ function. The patients were evaluated for response every 2 courses using standard oncologic criteria.

Objective response was achieved in 8 pts (26,6%) CR. 2 pts (6,6%), PR 6 pts (20%), SD 8 pts (26,6%), PD 14 pts (46,6%). The median duration of response was 5,8 months (range 2m-13m). The patients whom achieved CR, one of them with initial mts in lung, skin, relapsed twelve months after finished the treatment and the other with initial mts in liver, skin, nodes, spleen remained NED for 13 months.

Toxicity was moderate. The most commonly observed toxicities were nausea, vomiting and flu-like syndrome. 2 patients (6,6%) discontinued treatment for trombocytopenia G IV. The evaluation of the toxicity is showed 5 pts (16,6%) n/v G1, 4 pts (13,3%) G2, 1 pt (3.3%) G4. Flu like syndrome 9 pts (30%) G1, neutropenia 1 pt (3,3%) G1, 2 pts (6,6%) G2, 2 pts (6,6%) G3, anemia 2 pts (6,6%) G1, 1 pt (3,3%) G2, 1 pt (3,3%) G3 Diarrea 3 pts (10%) G1, 1 pt (3,3%) G4

**Conclusion:** The objective response with this combination was similar to the response with other treatment and only with a moderate toxicity.

## 593P Internal hemipelvectomy in children and youths with bone tumors.

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In the period of 1985-1999 more than 250 patients with primary bone malignant tumors (osteosarcoma, Ewing sarcoma, chondrosarcoma) were treated in the National Research Institute of Mother and Child in Warsaw. In all of them contemporary methods of complex treatment were applied, including chemotherapy, surgery and/or radiotherapy. Localization of the primary neoplasm's focus in the pelvis is less common and the radical surgery is problematic.

We present a group of 13 patients in whom following operations were performed:

- 2 "classical" hemipelvectomies: excision of pelvis bone with exarticulation of lower extremity,
- 11 internal hemipelvectomies: excision of pelvis bone sparing the lower extremity:
- 2 patients, type I: hip bone ala excision above the hip articulation,
- 1 patient, type II A: excision of the hip bone ala with the hip articulation,
- 2 patients, type II B: ischiadic and pubic bone excision with the hip articulation,
- 4 patients, type II C: excision of the hip bone ala with the hip articulation, pubic and ischiadic bones,
- 2 patients, type III: pubic and ischiadic bones excision under the hip articulation.

Internal hemipelvectomies have been made mainly in last two years. Ten patients are alive with the follow-up of 8-48 months. The patients have been rehabilitating the salvaged limb.

**Conclusions:**

1. The internal hemipelvectomy is a less mutilating operational treatment, performed within the complex therapy of malignant bone tumors in children and youths.
2. The internal hemipelvectomy allows limb salvage and the patient's walking
3. The internal hemipelvectomy requires a very well prepared operation team, good technical background allowing reconstruction of the resected bones and rehabilitation in the postoperational time.

## 594P Pelvic Ewing's sarcoma - 20 years experience.

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**Introduction:** Despite the improved survival of patients with Ewing's sarcoma, pelvic location remains a bad prognostic factor. This retrospective analysis tries to point out the reasons of such a situation, and to evaluate the impact of modern comprehensive approach on prognosis.

**Material and methods:** From 1977/2 to 1998/6, 53 patients have been treated by our group for Ewing's sarcoma of pelvic bones. 32 were males, 21 females aged 6 to 35 years (median 16.3). At first screening 15 patients had already metastases and 38 presented with localised disease. Treatment included chemotherapy for all patients according to the current protocol at the time of presentation: four drugs (vincristine - dactinomycin - cyclophosphamide, doxorubicin: V Ad CA, five drugs (VAd CA + ifosfamide) or six drugs association (IVAd CA + etoposide or cisplatinium). Local treatment used radiotherapy alone for 24 patients, surgery alone in 18 and a combination in 11 All patients have been followed up every 3 months for 2 years, every 6 months for 2 other years and then yearly.

**Results:** With a median follow up often years, the 5 year actuarial event free survival rate for all patients is 31%; 13% for primary metastatic patients and 40% for patients seen with localised disease ($p<0.001$) In primary localised tumor the major prognostic factors are the adequacy of surgical resection ($p<0.01$) and the high dose intensity of chemotherapy, particularly during the induction ($p<0.05$). Patients treated by radiotherapy had a 44% risk of local recurrence 17% life expectancy, and a 13 months median survival compared to an 80% life expectancy and 80 months median survival for patients after wide resection.

**Conclusion:** 1. Primary metastatic patients require new approach. 2. *Early wide resection* of the primary and *adequate dose intensity of a 6 drugs chemotherapy* give best results in pelvic Ewing's despite large tumoral volume or even incomplete response to preoperative chemotherapy.

## 595P High value of age in localised Ewing's sarcoma.

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**Introduction:** In Ewing's sarcoma, the prognostic value of age is debated Most early monocentric studies published disease free survival rate between 10% to 30% for adult patients compared to 20-60% for children. But other multicentric trials (IESS, CESS or SFOP) did not find such a difference. We imagined that the observed differences could be correlated with the given drug intensities and analysed our data to prove it.

**Material:** From 1986/1 to 1999/1, 48 patients with localised Ewing's sarcoma of bone have been treated by our team. They were 29 males and 19 females with a median age of 18 years (5-35) Chemotherapy started with a short bidrug induction (6 weeks of cyclophosphamide - doxorubicin) surgery in all cases (en bloc resection when feasible, curettage for vertebral and sacral locations). Post-operative chemotherapy used 5 or 6 drugs (vincristine - dactinomycine - ifosfamide - cyclophosphamide - doxorubicin or etoposide - cisplatinium) for 10 months. All patients have been followed up with physical examination, plain RXrays, bone scan, computed tomographies of the lungs and primary site every 3 months for 2 years, then every 6 months for 2 years and yearly then after

**Results:** With a median follow up of 7 years and 6 months, 37 (77%) patients are event free survivors. In this series, the site of the tumor and the tumoral volume had no impact on disease free survival but *only age, body surface area and response to preoperative chemotherapy*. The life expectancy of patients under 19 years is 96% (24/25) but only 56% (13/23) for patients 19 or older ($p < 0.001$). The disease free survival of patients with body surface area under 1.4 sqm is 100% compared to 55% for patients with larger surface ($p < 0.001$). The univariate analysis shows that received drug intensities of vincristine and dactinomycin are the only independent therapeutic prognostic factors (both correlated with age and body surface area). With the total dose limit of 2 mg for vincristine and 2 mg for dactinomycin patient with larger surface area (> 1.4 sqm) received less drugs by sqm than younger patients. In multivariate analysis, age had no prognostic value, but only the received drug intensities of vincristine and dactinomycin.

**Conclusion:** In Ewing's sarcoma, *age* is not an independent prognostic factor but only underlines the importance of given dose intensities of vincristine and dactinomycin.



 