non-specifically to DNA and NCI-COMPARE correlates ET743 with doxo, daunorubicin and morfholino-ADR. *In vivo*, ET-743 shows significant ANT in IP implanted B16 MEL and P388 leukaemia; moreover ET-743 is curative in nude mice bearing sc implanted early (up to 100% tumour free at 60 μg/kg/d/iv-qd × 4) and advanced (up to 40% tumour free animals at day 58 after implant) MX-1 breast ca xenografts respectively. The MTDs in mice, rat and dog have been determined. A clinical oriented formulation has been achieved and the identification of assay method is ongoing. Large scale supply of ET-743 is feasible by recollection and/or industrial culture of the tunicate (life cycle achieved). ET-743 will start phase I ecaluation in the U.S. and in Europe.

110 ORAL

AMIFOSTINE PROTECTS AGAINST CYCLOPHOSPHAMIDE AND CISPLATIN-INDUCED MUTAGENESIS WITHOUT AFFECTING THERAPEUTIC EFFECTIVENESS

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Cyclophosphamide and cisplatin, while extremely effective in killing tumor cells, are both highly mutagenic and carcinogenic to normal cells. When administered at doses ranging from 50 to 200 mg/kg to C3H mice, cyclophosphamide induced mutations at the *hprt* locus in splenocytes in a linear dose response manner, e.g., mutant frequency increased from 1.5 × 10^{-6} to 4 × 10^{-5}. Under similar conditions, pretreatment with amifostine protected against cyclophosphamide-induced mutagenesis. Mutant frequency was reduced from 1.6 × 10^{-5} to 1.8 × 10^{-6} with no reduction in the therapeutic response of cyclophosphamide on fibrosarcoma cells. Cisplatin at a dose of 4 mg/kg increased mutant frequency from 1.5 × 10^{-6} to 3 × 10^{-6}. Amifostine reduced this frequency back to control levels (i.e., 1.5 × 10^{-6}). Amifostine's anti-mutagenic effects are being monitored in a clinical trial of amifostine and high-dose cyclophosphamide. Data from this trial will be presented. Amifostine has a potential clinical role for antimutagenesis and anticarcinogenesis in radiation and/or chemotherapy protocols. Supported by Chicago Center for Radiation Therapy, DOE CONT W-31-109-ENG-38 and NIH CA-37435.

111 ORAL

PHASE I CLINICAL AND PHARMACOKINETIC TRIAL OF THE PODOPHYLLOTOXIN DERIVATIVE NK 611 USING AN ORAL DAILY ADMINISTRATION SCHEDULE

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We have performed a clinical and pharmacokinetic trial of the new podophyllotoxin derivative NK 611 administered orally for 21 days repeated every 35 days. Eighteen patients (pts) [9 female, 9 male; median age 60 years (37–73)] with histological proven solid tumors were enrolled in this study. Dose levels were 5 mg/day (105 mg absolute (abs)), 10 mg/day (210 mg abs), 12.5 mg/day 1 (262.5 mg abs) and 15 mg/day (315 mg abs) with a total of 39 courses administered. Toxicity has been evaluated by NCI-CTC criteria. At dose level 5 mg/day, no hematological toxicities (HT) were observed. At dose level 10 mg/day 2/6 pts developed °3 leukopenia (WBC), 1/6 pts °3 granulocytopenia (ANC), 1/6 pts °4 hemoglobin (Hb) and one pt thrombocytopenia (ptl) °2. At dose level 12.5 mg/day 1/8 pts developed °4 WBC, 4/8 pts °4 ANC, 2/8 pts °3 Hb and 1/8 °3 ptl. One pt at 15 mg/day showed °3 WBC, °4 ANC and °2 Hb and °2 ptl. Non-HT at dose level 10 mg/m^2 were 1/6 °2 pain, 1/6 °3 anorexia and 1/6 °4 dysphagia. Non-HT at dose level 12.5 mg/m^2 included 5/8 °2 alopecia, 1/8 °3 dyspnoea, 1/8 °2 fever, 1/8 °2 anorexia, 1/8 °2 nausea and 1/8 °2 vomiting. Non-HT at dose level 15 mg/m^2 (1. pt) consisted of neutropenic fever and °2 alopecia. Pharmacokinetic analysis of 6 pts treated with 12.5 mg qd are available. Using a 2-compartment model, $t_{1/2\alpha}$ ranged from 0.47 to 1.54 h, $t_{1/2\beta}$ ranged from 2.0–11.6 h. Mean Cmax was 1.477 ± 0.331 μg/ml. Mean AUC at 12.5 mg/m^2 was 13.666 ± 3.81 μg/ml·h. No objective tumor response was observed. The Maximum Tolerated Dose was 12.5 mg/d. Dose Limiting Toxicity was ANC °4. The recommended dose for clinical Phase II studies is 10 mg/m^2.- Supported by a grant from ASTA Medica AG

112 ORAL

CYCLIN D1 EXPRESSION IN OVARIAN CANCER: A POTENTIAL THERAPEUTIC APPROACH BY ANTISENSE OLIGOMERS

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Cyclin D1 (CD1) is a key regulator of the G1 phase of the cell cycle and is required for the progression to S-phase. CD1 has been found to be overexpressed in a variety of human tumors functioning like an oncogene. In the current study, the expression of CD1 in samples from patients bearing benign or malignant ovarian tumors has been investigated. Preliminary data, in 15 patients, indicate that the majority of carcinomas express higher levels of CD1 protein compared to benign neoplasms. Furthermore, 3 ovarian cancer cell lines have been used to study the effects induced by antisense oligonucleotides to CD1 gene, "*in vitro*". An 18 mer oligomer, complementary to the translation start site of the CD1 cDNA, has been synthesized and administered to the OVCAR-3 ovarian cancer cells at increasing concentrations. Significant inhibition of cell growth (55%) was reported at 401 μM after 3 days of culture. Equivalent effects were obtained with the SW626 and IGROV-1 cells resulting in 48% inhibition as compared to controls. In addition, a marked reduction of the mRNA and protein contents was reported. These preliminary results show the potential role of CD1 as a target for the control of ovarian cancer-growth by antisense oligomers.

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113 POSTER

MICROFILAMENT ACTIVITY (CELL DIVISION BLOCK) OF CYTOCHALASIN D AS A SENSITIVE PARAMETER FOR FUNCTIONAL P-GLYCOPROTEIN DETECTION

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Classical multidrug resistance (cMDR) and its reversal by MDR-modulating agents are of increasing clinical importance. However, the accurate detection of functional activity of the *mdr1* gene product P-glycoprotein (P-gp) is critical. We report here on the sensitivity and specificity of the cell division blocking activity of cytochalasin D (CD) as a parameter for actual P-gp transporting capacity by documenting that: (1) CD is a specific P-gp substrate (detected by drug-accumulation, drug-cytotoxicity, photaffinity-labelling) in a large panel of tumor cell lines (parental n = 9, resistant sublines n = 17) of different origin (men and animal, solid and hematopoietic) and degree of resistance (2.1- to 800-fold); (2) that the CD cell division blocking activity (determined by actin staining, microscopical evaluation of bi-multinucleated cells) is a sensitive parameter for P-gp activity as well as for its modulation evaluated by a large panel of chemically unrelated chemosensitizers (n = 26). For making the assay easily manageable it was automatized using FACS ploidy analysis. Correlations with common cMDR detection methods demonstrate the high sensitivity and specificity of the presented functional cMDR assay.

114 POSTER

IDARUBICIN AND DAUNORUBICIN BINDING TO DNA IN SENSITIVE AND RESISTANT LEUKEMIA K562 CELLS

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Idarubicin (IDA) is a most active anthracycline in treatment of acute myelogenous leukemias including those resistant to daunorubicin (DAU). To study this phenomenon we have compared IDA and DAU intracellular accumulation and binding to DNA in sensitive (sens) and resistant (res) human leukemia K562 cells and verapamil (Ver) influence on these parameters. It was shown: (1) binding to DNA of IDA in sens and res cells is higher than that of DAU; (2) both drugs' binding to DNA is about two times higher in sens than in res cells; (3) after Ver preincubation IDA (but not DAU) binding to DNA in res cells achieves about the same value as in sens cells. The results can explain the higher clinical efficacy of IDA than DAU in treatment of sens and res leukemias and allow supposition that IDA efficacy can be further elevated by its combination with Ver. Supported by UICC, International Soros Foundation and Russian Foundation of Basic Researches.