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protease inhibitor. Trastuzumab (Herceptin ®), a humanized antibody against HER2 ectodomain, at doses of 10-100 nM, also inhibited basal and induced HER2 cleavage. This inhibitory effect is specific of trastuzumab, since 2C4, another antibody against HER2 ECD, did not show any significant effect on constitutive receptor shedding. The inhibition of HER2 cleavage is not due to antibody-induced receptor downmodulation, given that trastuzumab inhibited HER2 cleavage at 30 min, and receptor downmodulation was not detected until 24 h. In addition, trastuzumab effectively prevented HER2 shedding in cells where receptor internalization was inhibited by hypertonic treatment. Finally, an increase in the phosphotyrosine content of full-length HER2 was associated with APMA-induced cleavage in BT-474 cells, and this increase was less pronounced if trastuzumab was present. These data indicate that trastuzumab has a direct inhibitory effect on HER2 shedding that could contribute to its therapeutic properties.

606O A phase I and pharmacological study of CCI-779, a rapamycin ester cell cycle inhibitor.

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CCI-779 is an ester of rapamycin which inhibits the cell cycle. The agent inhibits the activity of mTOR (mammalian target of rapamycin) and disrupts key signal transduction pathways, including those regulated by the p70s6 and PHAS-I kinases resulting in cell cycle arrest at the G1-S boundary. This study is evaluating the feasibility, pharmacokinetics and biological effects of escalating doses of CCI-779 administered as a 30-minute IV infusion daily x 5 every 2 weeks to patients (pts) with solid neoplasms. Fifty-one pts have received 262 courses (median 4, range 1-16) at doses ranging from 0.75-19.1 mg/m^2/d. Three episodes of DLT have been observed in the 1st cycle so far consisting of asymptomatic, grade 3 hypocalcemia at the 2.16 mg/m^2/d dose level (1 pt), grade 3 elevation in transaminases (1 pt), and grade 3 vomiting, grade 2 diarrhea and grade 2 asthenia (1 pt) at the 19.1 mg/m^2/d. Grade 3 thrombocytopenia requiring dose reduction was observed in 3 heavily-pretreated (HP) pts at the 19.1 mg/m^2/d dose level, indicating that this dose is not well-tolerated in HP subjects. At this juncture, HP patients are receiving 15 mg/m^2, while doses continue to be escalated in minimally-pretreated pts. Other toxicities noted, generally mild-moderate, some over a broad dose range, include neutropenia, rash, mucositis, asthenia, fever, and hypertriglyceridemia. Allergic phenomena have also being observed. In 17 pts receiving doses of 0.75-3.12 mg/m^2/d, CCI-779 exhibited increasing peak concentrations with increasing dose, preferential red blood cell partitioning, and a median terminal half-life of 15.2 h. One patient with NSCLC achieved a PR. Minor antitumor responses and/or prolonged (> 4 months) stable disease have been noted in several drug-refractory cancers including: soft-tissue sarcoma (3), and cervical (1), uterine (1), and renal cell (3) carcinomas. CCI-779 dose escalation-expansion continues. The toxicity profile and antitumor activity observed to date are encouraging.

607O Phase I study of the gene therapy prodrug, CB1954.

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CB1954 (5-(aziridin-1-yl)-2,4-dinitrobenzamide), a substrate for the bacterial enzyme nitroreductase, is converted into a potent bifunctional alkylating agent. CB1954 is a candidate prodrug in virus-directed, enzyme prodrug therapy (VDEPT) protocols. CB1954 was administered by bolus intravenous (IV) injection on a 3-weekly cycle, or intraperitoneally (IP) followed by 3-weekly IV injections, with a maximum of six cycles of drug. 30 patients were treated, age range (23-78 years, median 62 years). 19 patients were males. 22 patients received IV CB1954, 8 patients had IP CB1954, 4 of whom also received IV drug. 13 cases were colorectal cancers, 4 gastric, 3 oesophageal, 3 mesotheliomas, with ovarian, pancreatic and unknown primaries accounting for the remainder. The first dose level was 3mg/m^2, no significant toxicity was seen until the fifth dose level of 24mg/m^2. The maximum tolerated dose IV was 37.5mg/m^2 with gastro-intestinal and hepatic dose-limiting toxicities (DLT). No DLT has been seen in the IP regime at the current dose of 24mg/m^2. No alopecia, marrow suppression or nephrotoxicity was observed. No clinical response was seen. CB1954 pharmacokinetics indicated a linear relationship between dose and area under the curve for the IV dose range of 3-24mg/m^2, with a non-linear effect at higher doses. Mean elimination half-life was 17 minutes with <5% renal excretion. Animal data suggests biliary excretion as the main clearance mechanism. Serum levels after IV administration (30mg/m^2), persisted between 10 and 1μM for 2 hours. IP administration (24mg/m^2) achieved peritoneal levels between 100 and 1μM for 18 hours. The IC50 for CB1954 in cancer cells expressing nitroreductase ranges from 0.1 and 10 μM. In summary, CB1954 is a well-tolerated prodrug and sufficient serum/peritoneal levels are generated for a VDEPT approach to be feasible. We are now conducting a phase I trial of adenovirally delivered nitroreductase and IV CB1954 in patients with primary/secondary liver tumours.

608PD Phase I and pharmacokinetic study of BIBX 1382, an EGFR inhibitor, as continuous daily oral administration.

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The pyrimido-pyrimidine BIBX 1382 inhibits the intracellular tyrosine kinase domaine of the epidermal growth factor receptor (EGFR), thus specifically reverting the aberrant enzymatic activity from overexpressed and constitutively activated EGFR, respectively. A modified Fibonacci scheme was used to escalate the daily oral dose; the following dosages and cycles (defined as *treatment during 28 days*) were applied, respectively *25mg 6, 50mg: 2;* 100mg 5; 200mg: 7, 150mg: 3. Over a 10 months accrual phase, 11 pts (7 females, 4 males) with a median age of 63 years (50-73), WHO PS 0:5, 1 6 and miscellaneous solid tumors were entered. The number of cycles applied per pt was median 1 5 (0-7). Reversible, dose-dependent increase of liver enzymes (maximal CTC grades: GGT: 4, SGOT: 3, SGPT: 3, aP: 3, bilirubin: 3) prevented regularly from further dose escalation. Oral medication yielded plasma levels far below expected to be efficacious. Realistically, target plasma levels could not be reached via the oral route at reasonable dosage. Meanwhile, a preclinically unknown metabolite was identified from urine of one patient. Subsequently, this metabolite was found to be abundant in patient plasma. The metabolite was demonstrated to be pharmacologically inactive. Due to dose limiting increase of liver enzymes, low bioavailability of BIBX 1382 and detection of a pharmacologically inactive metabolite this trial was discontinued.

609PD A phase I and pharmacologic trial of weekly epothilone B in patients with advanced malignancies.

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Epothilone B (EB) is a naturally occurring macrolide that is a more potent microtubule stabilizer than paclitaxel and exhibits a broad range of preclinical anti-tumor activity at pg/ml levels. EB is also active in paclitaxel-resistant models. A phase I dose-escalating trial of weekly intravenous administration of EB was undertaken to determine toxicities, to identify a maximum-tolerated dose, and to assess pharmacokinetics. Patients receive weekly infusions of EB every 6 out of 9 weeks and are enrolled in cohorts of 3 or more using a Fibonacci-based dose escalation strategy. 24 patients have been enrolled to date at doses ranging from 0.3mg/m^2 to 1.85mg/m^2. Only one patient has developed grade 3 toxicity with parasthesia to date at dose level 2 (0.5mg/m^2). Pharmacokinetic results are presented.

Dose mg/m^2	Week	AUC_{INF} ng h/ml	C_{max} mg/ml	CL mg/min	Vss L	$T_{1/2}$ H
0.3	1	28	15	462	1201	64
0.3	6	187	14	-	-	73
0.5	1	85	14	254	1179	83
0.5	6	312	28	-	-	103
0.75	1	189	18	189	820	58
0.75	6	153	19	-	-	63
1.1	1	204	23	185	843	59
1.1	6	NA	NA	-	-	NA

At the initial dose level, drug accumulation was observed with an accumulation ratio ($AUC_{0\text{-}50h\ dose\ 6}/AUC_{0\text{-}50h\ dose\ 1}$) of 2.45. Continued dose escalation is planned.