Rhabdastrellic acid-A in HL-60 cells. Activation of downstream molecule of PI3K pathway such as AKT also was inhibited following Rhabdastrellic acid-A treatment.
Conclusion: It concludes from these results that Rhabdastrellic acid-A inhibits PI3K/Akt survival pathway and induces caspase-3-dependent apoptosis in leukemia cells.

375 POSTER

HIV-1 protease inhibitor induces growth arrest and apoptosis of human prostate cancer cells in conjunction with blockade of androgen receptor, STAT3, and AKT signaling

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This study found that HIV-1 protease inhibitors (PIs), including nelfinavir, ritonavir, and saquinavir induced growth arrest and apoptosis of human prostate cancer cells (LNCaP, DU145 and PC-3 cells), as measured by MTT and TUNEL assay, respectively on the third day of culture. In addition, PIs blocked androgen receptor (AR) signaling in association with down-regulation of nuclear levels of AR in LNCaP cells as measured by reporter assay and Western blot analysis. As expected, PIs down-regulated the level of the AR target molecule prostate specific antigen in these cells. Moreover, PIs disrupted STAT3 signaling; PIs blocked IL-6-induced phosphorylation of STAT3 and inhibited STAT3 DNA binding activity in LNCaP and DU145 cells, as measured by Western blot analysis and ELISA-based assay, respectively. Furthermore, PIs blocked AKT signaling in prostate cancer cells as measured by kinase assay with GSK-3α /β as a substrate. Taken together, PIs inhibited proliferation of prostate cancer cells in conjunction with blockade of signaling by AR, STAT3, and AKT suggesting that this family of compounds might be useful for the treatment of individuals with prostate cancer.

376 POSTER

Tolerability results with the novel oral prenyl transferase inhibitor AZD3409 following single and multiple doses in volunteer studies

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Background: AZD3409 is a novel, oral, antitumour agent that acts as a prenyl transferase inhibitor. Here we report preliminary results of the tolerability assessments conducted during two studies of AZD3409 in healthy human volunteers.
Methods: In the single ascending dose study, a maximum of eight healthy male volunteers were dosed at each dose level (6 active, 2 placebo) in a randomised, double-blind, alternating panel design with doses escalated from 20 mg to 2500 mg. In the multiple dose study, a maximum of 16 volunteers (12 active, 4 placebo) were administered the same once-daily dose for 7 consecutive days at the following ascending doses for three consecutive cohorts: 500 mg, 1000 mg, and 1750 mg. The following were monitored: vital signs, ECG, clinical chemistry, haematology and urinalysis, and adverse events for 21 days after each dose. Data remain blinded and the analysis is ongoing.
Results: The maximum tolerated single dose of AZD3409 was 1750 mg, which was also tolerated on multiple dosing. In the multiple dose study, there have been no significant safety or tolerability issues identified with 500 mg, 1000 mg, or 1750 mg multiple doses. Possible drug-related adverse events include loose stools, abdominal discomfort, light-headedness, nausea, and transient rash. These adverse events were generally mild (CTC grade 1) and resolved without treatment. One subject in each of the 1000 mg and 1750 mg cohorts had loose stools graded as moderate (CTC grade 2) in the first half of the dosing week. The 'moderate severity' grading lasted no more than 1 day in both cases and both volunteers completed the full 7-day treatment schedule. The incidence, but not the severity, of gastrointestinal adverse events appears to correlate with increasing dose. No clinically important changes in clinical assessment, ECG, or routine laboratory safety data have been detected.
Conclusions: Based upon these results, 1750 mg of AZD3409 once daily for 7 days is well tolerated in healthy volunteers.

377 POSTER

Tolerability and limited activity of perifosine in patients with advanced soft tissue sarcoma (STS): a multi-center phase 2 consortium (P2C) study

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Background: Current treatments in STS are largely palliative and novel agents need exploration to improve patient (pt) outcome. A prolonged (>12 mos) objective response in a refractory STS pt during a phase I trial prompted our phase II evaluation of the 6-month progression-free rate of perifosine in pts with advanced STS. The study design required 4 of 15 evaluable pts to be progression-free at 6 mos. to enroll 27 additional pts.
Methods: Pts received a perifosine loading dose of 150 mg p.o. every 6 hours $\times$ 4 for day 1, followed by 100 mg once daily for d2–28. Subsequent 28 day cycles were the same, excluding the loading dose. Eligible pts had measurable disease and adequate organ function (total bilirubin and creatinine $\leqslant$ UNL, PLT > 100,000 μL, ANC > 1,500 μL). Serum was collected for PK analyses.
Results: 23 pts were enrolled. A majority had prior treatment: 1–2 chemotherapy regimens (87%), surgery (96%), and radiotherapy (52%). 22% presented with liver metastasis. Pts are aged 24–77 yrs (median 53); 65% are female; and a majority (56%) ECOG PS 1 (vs 0). 19 of 23 pts received at least 2 cycles of therapy (range 2–8). All pts are evaluable for toxicity. One pt had Gr. 4 ileus. 6 pts (26%) had Gr. 3 toxicity, including fatigue (2 pts) and 1 patient each of anemia, infection, muscle weakness, pain, rash, anorexia, dehydration, and diarrhea. 6 pts (26%) have died, all of which are non-treatment related. A pt having myxosarcoma had a partial response lasting 5+ mos. Two (1-myxosarcoma, 1-desmoid) pts are progression-free at 6 months [15%, 95% CI (2–41%)].
Conclusions: Although this study failed to satisfy the criteria to proceed with accrual, the regimen was tolerable. The preliminary observation of another potential prolonged responder raises the question of whether specific histologies or tumor characteristics might predict a more sensitive sub-population of STS pts. PK analyses are underway. Supported by N01-CM-17104.

378 POSTER

In vivo and in vitro enhanced antitumor activity of Oxaliplatin in combination with cetuximab (C225), a chimeric monoclonal antibody anti-epidermal growth factor receptor on a panel of human colorectal tumor xenografts

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Advanced colorectal carcinoma is a major cause of morbidity and mortality in the developed countries. Colorectal cancers frequently express the epidermal growth factor receptor (EGFR), which has been correlated with more aggressive disease and poor prognosis. Several EGFR inhibitors such as C225 (cetuximab), a chimeric anti-EGFR monoclonal antibody, are being developed in various indications. Oxaliplatin (L-OHP), is a major compound in the treatment of colorectal carcinoma but has not been yet evaluated in preclinical studies in association with C225.These two drugs have demonstrated efficacy as single agent in the inhibition of tumor growth and apoptosis induction in colon cancer *in vivo* and *in vitro*.
The aim of our study was to evaluate the effect of the combination of C225 and L-OHP on a panel of L-OHP-insensitive colon cancer cell lines.
These studies were performed both *in vivo* and *in vitro* on 4 colon cancer cell lines HCT-8; HT-29, SW620, HCT-116 showing different levels of EGF-R expression in WB analysis. We first assessed the cell growth and IC_{50} of L-OHP, C225 monotherapy or combination of both. The combination of L-OHP and C225 led us to observe an inhibition of tumor growth and a decrease in IC_{50} of L-OHP in HCT-8, and HT-29. On the other hand, the combination of C225 and L-OHP did not show any major modification in IC50 of L-OHP in SW 620 (EGF-R negative) or in HCT-116 (EGF-R positive).
Xenografts in nude mice were established by subcutaneous injection of 10 $X10^6$ human colon cancer cells in both flanks. Mice were then randomized into four treatment groups: control, anti-EGFR (C225), L-OHP or C225 plus L-OHP. C225 was administered i.p. at the dose of 0.5 mg. three times a week. L-OHP was infused at the dose of 10 mg/kg by i.v. route 7 days after implantation.The combination of C225 (0.5 mg) and L-OHP (10 mg/kg) strongly inhibited the growth of HCT-8 and had a slight effect on HT-29 established tumors. In a refractory tumor model SW620 and HCT-116, the