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CBP501, a novel cell cycle G2 checkpoint abrogator. Preliminary results of the initial phase I and pharmacokinetic (PK)/ pharmacodynamic (PD) study in patients (pts) with advanced solid tumors

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Background: The loss of the G1 checkpoint function in most tumors makes cancer cells more dependant on G2 checkpoint. CBP501, a specifically designed duodecapeptide comprised entirely of D-amino acids, is a G2 checkpoint abrogator which inhibits phosphorylation of Ser^{216} on Cdc25C in a time and dose dependent manner. CBP501 has exhibited activity in a variety of tumor models alone and in combination with DNA damaging agents. We report the first single-agent phase I dose-escalation trial in patients with solid tumors, intended to determine maximum tolerated dose (MTD) and dose-limiting toxicity (DLT), and assess safety, PK and PD profile, and preliminary evidence of efficacy.
Material and Methods: CBP501 is given by 60 min IV on days 1, 8, 15 every 28 days. Three dose levels (DL) have been explored so far (0.9, 1.8 and 3.6 mg/m^2). Diphenhydramine 50 mg IV was given prophylactically due to preclinical observation of histamine release syndrome. Cardiac monitoring is undertaken via LVEF, ECG and cardiac enzymes. CBP501 PK and PD are assessed on days 1 and 15 of cycle 1. PD assesses levels of phosphoserine 216 of CDC25C in peripheral blood lymphocytes. MTD is defined as the level below the one where 2 out of 3–6 patients present DLT in cycle 1 or 2.
Results: Between June 2005 and May 2006, 10 pts have been treated. Male/female: 7/3; median age 61 years (47−67); PS 0/1: 4/6; tumor types: colon (3 pts), pancreas (3), ovarian (2), melanoma (1), renal (1). Pts were pretreated with a median of 4 (2−7) prior chemotherapy regimens. In 9 pts evaluable for MTD determination (1 early PD): 17 cycles have been administered for a median of 2 cycles per pt (range 1−2+); 8 pts have discontinued for disease progression. Toxicity is limited to grade 1–2 events (see Table). PK has been assessed in 7 pts after infusion 1 and 3: mean (±sd) C_{max} (ng/mL) in dose levels 1 and 2: 125 (6), 516 (192); AUC_{0-inf} (ng.h/mL): 145 (26), 824 (300); half-life (h): 0.7 (0.4), 1.1 (0.4). PK following infusion 3 was comparable Decreases in the rate of phosphorylation of Cdc25C were observed in 3/5 pts (DL1: 2/4, DL2: 1/1).

Related adverse events	NCI-CTCAE grade per patient	DL1: 0.9 mg/m^2 (N = 3)	DL2: 1.8 mg/m^2 (N = 3)	DL3: 3.6 mg/m^2 (N = 3)
Thrombocytopenia	1	1	–	–
Anemia	2	–	–	1
Nausea	1	1	1	–
Fatigue	2	2	–	–
Rash	1	1	1	–

Conclusion: CBP501 has been tolerated up to a dose of 3.6 mg/m^2 without DLT, and some evidence of biological activity has been observed. Dose escalation is ongoing, and trials of CBP501 in combination are being initiated.

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The RANK ligand inhibitor OPG-Fc reduces bone lesions and skeletal tumor burden in the MDA-231 breast cancer and PC3 prostate cancer experimental osteolytic metastases models

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Background: Bone metastases are a frequent complication of cancer and are commonly observed in patients with advanced breast and prostate cancer. In lytic bone metastases, tumor cells interact with the bone microenvironment to induce osteoclastogenesis, leading to bone destruction. RANK ligand (RANKL) is essential for osteoclast formation, function, and survival. Tumor cell-mediated osteolysis is thought to occur ultimately via induction of RANKL within the bone stroma, and inhibition of RANKL in animal models of breast cancer metastases blocks tumor-induced osteolysis and prevents the progression of skeletal tumor burden (Morony et al., 2001). The aims of this study were to define the mechanisms of the antitumor effect of RANKL inhibition on skeletal metastases and to test if similar effects are observed in both breast and prostate cancer-induced osteolysis.
Methods: We first examined the effects of the RANK ligand inhibitor OPG-Fc on tumor-induced osteolysis and tumor burden in mice inoculated with PC3 prostate cancer or MDA-MB-231 breast cancer cells. Tumor-bearing mice received OPG-Fc subcutaneously (3 mg/kg, 3×/week). To examine the potential mechanisms underlying the reduction in tumor burden, levels of proliferation and apoptosis markers in established breast tumors, taken from mice treated with OPG-Fc over 5 days, were analyzed by immunostaining. Alterations in bone were analyzed by radiographic analysis, histomorphometry, or serum TRAP5b measurements.
Results: Radiographic analysis on day 28 indicated that OPG-Fc treatment prevented the progression of tumor-induced osteolysis. Serological, histological, and histomorphometric analyses also revealed that OPG-Fc treatment eliminated mature and immature osteoclasts, reduced tumor-induced bone resorption, and reduced osseous tumor burden. Comparable results were obtained after OPG-Fc treatment of mice with established skeletal PC3 prostate tumors and osteolytic lesions. Short-term OPG-Fc treatment substantially reduced tumor cell histone H3 phosphorylation and increased activated caspase-3. Increased activated caspase-3 and decreased phospho-histone H3 levels were also observed in MDA-MB-231 skeletal tumors after combined treatment with OPG-Fc and the cytotoxic agent cytoxan.
Conclusions: The significant reduction in skeletal breast or prostate tumor burden observed after OPG-Fc treatment appears to be due to a reduction in the growth rate and survival of tumor cells, indicating that RANKL inhibition may reduce tumor proliferation and increase tumor cell apoptosis within bone.

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A phase I study of wild-type reovirus, which selectively replicates in cells expressing activated Ras, administered intravenously to patients with advanced cancer

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Background: Reovirus is a double-stranded RNA virus with minimal pathogenicity in humans that selectively replicates in cells with activated Ras, sparing normal cells. Activated Ras inhibits the anti-viral effects of double stranded RNA-activated protein kinase. Reovirus serotype 3 Dearing has selective antitumor activity, both in vitro and in tumor xenograft models.
Material and Methods: Reolysin was administered as a 1-hour IV infusion every 4 weeks, initially for one day; then 3 days, then 5 days every 4 weeks. The starting dose was 1×10^8 tissue culture infectious dose (TCID50) increasing in successive cohorts until the observation of drug-related toxicity ⩾ grade 2. Endpoints were safety, detection of viral replication, viral shedding, evaluation of immune response and antitumor activity.
Results: A total of 29 patients (pts) (22 males; median age 54; ECOG performance status (PS) 0 = 12, PS 1 = 17) were treated. Pts were entered into 8 cohorts at the following dose levels: 1×10^8 for 1-day, 1×10^8 for 3-days, and 1×10^8, 3×10^8, 1×10^9, 3×10^9, 1×10^{10} and 3×10^{10} TCID50 for 5-days. A maximum tolerated dose (MTD) was not reached and no dose-limiting toxicities were observed. Toxicities were mild (grade 1 or 2) and included chills, fever, headache, rhinorrhea, fatigue and myelosuppression. Reverse transcription polymerase chain reaction (RT-PCR) studies of blood, urine, stool and sputum post reovirus administration and every week thereafter were negative for viral shedding for all treated pts. 63% of pts showed pre-existing anti-reovirus antibodies. Titres increased after 1-week of treatment and remained high during subsequent courses of treatment. One pt with metastatic prostate cancer had a 50% decrease in PSA after treatment at 3×10^9 TCID50, with evidence of tumor necrosis on CT scanning. Intratumoral reovirus replication was detected by electron microscopy in tumor biopsies. Two pts with metastatic colorectal cancer treated at 3×10^8 and 3×10^9 TCID50 had CEA tumour marker reductions of 60% and 27%, and received 6 and 3 courses of treatment respectively. One pt with metastatic bladder cancer treated at 1×10^9 TCID50 had a minor response and received 4 courses of treatment.
Conclusions: Reolysin is well tolerated with minimal toxicity. No MTD was reached. Virus-induced tumor necrosis associated with intratumoral viral replication after systemic delivery was observed. Encouraging hints of antitumoral activity were observed. Phase II studies are planned.