been implicated in many cancers by mutational activation of PI3Kα, loss of function of PTEN and/or activation of upstream receptor tyrosine kinases. PF-04691502 is an orally available dual-specificity inhibitor of PI3K and mTOR which has shown potent and selective activity in *in vitro* (biochemical, cell) and xenograft models.
Methods: PF-04691502 is administered to adult patients with advanced solid tumors orally once daily (QD) continuously, starting with a dose of 2 mg QD. Assessments include safety (NCI CTC AE v4.0), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity. Dose escalation occurs in 100% increments in 3-patient cohorts until a Dose Limiting Toxicity (DLT) or two grade 2 non-tumor related adverse events (AEs) are observed in the first cycle, at which point dose escalation is changed to no more than 40% increments until the DLT rate reaches or exceeds 33%. PD assessments include blood glucose and insulin. Antitumor activity is assessed per RECIST v1.1.
Results: As of 17 May 2010, a total of 8 patients have been dosed at 2, 4, and 8 mg QD. Tumor types have included NSCLC (2), breast, gastric, melanoma, ovarian, CRC and sarcoma (one each). PF-04691502 has been well tolerated with the most common treatment-related AEs being nausea, fatigue, headache and vomiting. Treatment-related AEs have been mostly mild to moderate (grade 1−2). One patient has experienced DLT (grade 3 fatigue) at the 8 mg QD dose level. Preliminary PK data indicate that PF-04691502 is eliminated with a half life of approximately 11−15 hours, with low clearance and a relatively high volume of distribution. At steady state, plasma concentrations exceed that estimated to be required for 50% suppression of phosphorylation of Akt, based on preclinical predictions. Minor changes in blood glucose and insulin have intermittently been observed. No objective tumor response has been observed. Dose evaluation continues.
Conclusions: Daily oral administration of PF-04691502 appears safe and tolerable across multiple dose levels. Nausea, fatigue and headache are the most frequently reported treatment-related AEs, those with only mild to moderate severity. To date one DLT (grade 3 fatigue) has been reported in a patient receiving 8 mg QD. Updated data for safety, PK, PD and antitumor activity will be presented.

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Phase 1/2 trial of CF102, a selective A3 adenosine receptor (A3AR) agonist, in patients with hepatocellular carcinoma (HCC)

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Background: CF102, a novel, orally-active, A_3AR agonist which induces tumor cell apoptosis in HCC experimental animal models, is under evaluation in this trial for the treatment of HCC patients with incurable disease.
Methods: The objectives of this trial are to evaluate the safety and pharmacokinetic (PK) behavior of CF102 in HCC patients. Utilizing a "3 + 3" design, successive cohorts of patients with advanced HCC were enrolled at CF 102 doses of 1, 5, or 25 mg twice daily, given orally in continuous cycles of 28 days each. Progression to a higher-dose cohort was based on first cycle toxicity. Standard safety and PK assessments were performed; α-fetoprotein (AFP) levels were obtained each cycle, and tumor imaging was obtained every other cycle.
Results: 9 patients (5 males), median age 75 (63−90) years, Child–Pugh Class A or B, have been administered CF102 across 3 cohorts, 3 at each dose level. No dose-limiting toxicities specifically attributed to CF102 have been observed at any dose level. Through 3 cohorts, with a maximum exposure of 8 cycles, adverse events reported in at least 2 subjects were: anorexia (5 subjects); abdominal pain, asthenia (4 each); diarrhea (3); and leg edema/swelling, fatigue, fever, nausea, back pain, chest pain, leg pain (2 each). All events classified as drug-related were either grade 1 or 2. No drug-related abnormalities of hematologic, renal, or hepatic function have been observed on laboratory testing. CF101 has shown good oral bioavailability and linear PK behavior after single doses and at steady state. To date, one patient, at the lowest dose level, has shown stable disease for 6 cycles accompanied by complete clinical regression of biopsy-proven skin metastases and a sustained fall in AFP. Furthermore, another patient infected with hepatitis C virus experienced a 1.4 $\log_{10}$ drop in viral titer during dosing with CF102.
Conclusions: Daily oral CF102 is safe and well tolerated at doses up to 25 mg twice daily, and shows linear PK in patients with HCC. CF102 has shown preliminary evidence of clinical activity in HCC patients based on clinical observations of stable disease and AFP reduction. The observation of a decrease in hepatitis C viral load is consistent with CF102's known preclinical anti-viral activity. A_3AR agonist treatment appears to hold promise as a novel therapeutic strategy in the treatment of advanced HCC and related liver diseases, and enrollment in the dose-confirmation phase of this trial continues.

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A first in human phase 1 study of the safety and pharmacokinetics of a novel Cdc7 inhibitor NMS-1116354, administered orally to patients with solid tumors

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Background: NMS-1116354 is a potent oral inhibitor of the serine-threonine kinase Cdc7. Cdc7 promotes DNA replication and is often upregulated in cancer. In vitro, NMS-1116354 inhibits initiation of DNA replication resulting in cell cycle arrest and apoptotic tumor cell death and causes tumor growth inhibition or regression in multiple human xenograft tumor models.
Methods: Patients with advanced solid malignancies are enrolled in successive cohorts using a 3+3 design to receive NMS-1116354 orally once daily for 7 days followed by a 7 day rest period (2-week cycle). Dose-limiting toxicities (DLTs) are determined during the first cycle and are defined as grade 4 (g4) neutropenia for >7 days, febrile neutropenia, neutropenic infection, g4 thrombocytopenia (PLT), g3 PLT for >7 days or with bleeding, any g3/4 non-hematologic toxicities representing a shift of 2 grades from baseline, failure to administer 70% of NMS-1116354 in cycle 1, >2 week-delay in starting cycle 2. Pharmacokinetics on days 1 and 7 in cycle 1, pharmacodynamic modulation of Mcm2 phosphorylation and gene expression in skin biopsies and Mcl-1 level in leukocytes in cycle 1 are evaluated. Tumor response by RECIST is assessed every 8 weeks.
Results: To date, 13 patients with metastatic cancer (4 males; median age: 62 [39−73]; median ECOG PS: 1 [0−1]) were treated in 4 dose levels (3, 6, 12 and 24 mg/m^2/day) and received a total of 50+ cycles (median 3, range 1−8). Primary tumor types were: colon (3), lung (2), breast (2), prostate, sarcoma, pancreas, carcinoid, thyroid and ovarian (1, each). All toxicities reported so far were of grade 1−2 in severity or representing a shift of 1 grade from baseline, allowing for continuing dose escalation as per the accelerated dose titration design. Potential drug-related AEs were fatigue (3 pts), anorexia, constipation, dry mouth and nausea (1 pt each). No cycle 1 DLTs observed. Current PK data suggest Cmax and AUC increase with the dose. Preliminary signs of pharmacodynamic modulation, such as Mcl-1 down-regulation in leukocytes, were observed in surrogate tissues. Two patients with colon cancer remained stable for 8 cycles (16 weeks).
Conclusions: In this Phase 1 study, NMS-1116354 is well tolerated. The MTD has not yet been established and dose escalation is ongoing, with 48 mg/m^2/day being tested.

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Phase I study of the vascular disrupting agent (VDA) ombrabulin (Ob) in combination with taxanes (T) and platinum salts (PS) in patients (pts) with advanced solid tumors

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Background: Ob is a tubulin binding VDA, derivative of Combretastatin A4. In preclinical studies synergy between Ob and T or PS has been observed.
Methods: Study objectives were to determine the recommended dose (RD), Dose-Limiting Toxicities (DLTs), safety and pharmacokinetics (PK), preliminary anti-tumor activity, potential predictive biomarkers of the combination of Ob with T (docetaxel D or paclitaxel P) and PS (cisplatin C or carboplatin Cb respectively) once every 3 weeks in pts who received a maximum of one previous line of chemotherapy (CT) for advanced disease.
Results: Forty-three pts (M/F 14/29), median age 51 (range 24−74), including 25 chemonaive pts (58%) were treated in 4 cohorts: I (Ob/C75 mg/m^2 day (d)1, D60 or 75 mg/m^2 d2 − 13 pts), II (Ob d1, C75/D75 d2 − 12 pts), III (Ob d1, CbAUC5/P175 d2 − 11 pts) and IV (Ob d1, CbAUC6/P200 d2 − 7 pts). Granulocyte growth factors were systematically administered as primary prophylaxis in cohort I and II. Dose levels (DLs) tested for Ob were: 15.5, 20, 25, 30, 35 mg/m^2.

The most common tumor types were lung (n = 11), breast (n = 11), and ovary (n = 5).
Cohort I is completed, the median number of cycles was 6 (range 1−9) and the RD is Ob20/C75/D75 mg/m^2. Two DLTs (febrile neutropenia and pulmonary embolism) were reported at cycle 1 of DL 25/75/75 mg/m^2.
Cohorts II, III and IV are under evaluation.
Other clinically significant gr 3/4 study drug related adverse events were: diarrhea, asthenia, drug hypersensitivity (2 pts each), transaminase increase, hypocalcemia, vomiting, nausea, peripheral neuropathy (1 pt each). Related cardiovascular events consisted on: gr 2 thrombo-phlebitis (3 pts), gr 2 left ventricular function decrease, gr 3 peripheral ischemia, gr 3 troponin increase and gr 2 hypertension (1 pt each).
Hematotoxicity was typical for T and PS combinations.
Objective responses were observed: one complete response (pt with triple negative breast cancer), 7 partial responses (3 lung including one pt with squamous histology, 3 breast and 1 ovarian cancer) and 21 pts had stable disease.
Preliminary results of PK and biomarkers studies will be provided.
Conclusion: Combinations of Ob with T and PS are feasible and well tolerated, with preliminary encouraging evidence of anti-tumor activity. Further studies in specific tumor types are planned.

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First-in-human study of PF-05212384, a small molecule intravenous dual inhibitor of PI3K and mTOR in patients with advanced cancer: preliminary report on safety and pharmacokinetics

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Background: The PI3K/mTOR pathway regulates cell growth, proliferation, glucose metabolism and survival. It has been implicated in many human cancers by mutational activation of PI3Kα, loss of function of PTEN and/or activation of upstream receptor tyrosine kinases. PF-05212384 is an intravenous dual-specificity inhibitor of PI3K and mTOR that has potent and selective activity in *in vitro* and xenograft models. A first-in-human phase 1 dose-escalation study is ongoing.
Methods: PF-05212384 is administered intravenously to adult patients with advanced solid tumors once weekly; the starting dose was 10 mg. Endpoints include safety (NCI CTC AE v4.0), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity. A modified continual reassessment method (CRM) targeting a 25% DLT rate is employed for the dose escalation phase. Patients have been enrolled in cohorts of 2 to 4 with dose assignment based on the adverse event profile of the previous cohorts; increments may range from 20% to 107%. PD assessments include blood glucose and insulin. Antitumor activity is assessed per RECIST version 1.1.
Results: As of 29 May 2010, 12 patients have been dosed at 10, 21, and 43 mg. Median age 54, median ECOG PS 1. Represented tumor types have included CRC (3), NSCLC (2), sarcoma (2), breast, pancreatic, esophageal, RCC, and salivary gland (1 each). PF-05212384 has been well tolerated, with the most common treatment-related AEs being nausea, hyperglycemia, and fatigue. Treatment-related AEs have all been mild to moderate (CTC AE grade 1−2). No patients have experienced DLT and dose escalation is ongoing. Preliminary PK data indicate that PF-05212384 is eliminated with a half-life of approximately 16 hours, with low clearance and a relatively high volume of distribution. At steady state, plasma concentrations exceed those estimated to be required for suppression of phosphorylation of PI3K/mTOR pathway substrates and induction of apoptosis, based on preclinical predictions. Changes in blood glucose and insulin have been observed in some but not all patients. No objective tumor responses have been observed.
Conclusions: Weekly administration of PF-05212384 is safe and tolerable in early dose levels. Nausea, hyperglycemia, and fatigue of mild to moderate severity are the most frequently reported treatment-related AEs. To date no DLTs have been reported and dose escalation continues. Updated data for safety, PK, PD and antitumor activity will be presented.

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Imetelstat sodium (GRN163L), a telomerase inhibitor: tolerability, pharmacokinetics and pharmacodynamic activity using an intermittent once every four weeks dosing schedule in patients with advanced solid tumors

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Background: Telomerase is upregulated in tumor cells and particularly cancer progenitor cells where it is required for maintenance of telomere length and limitless replication. GRN163L is a potent, lipidated 13-mer oligonucleotide inhibitor of telomerase and is the first agent in clinical trials to target telomerase. Previous reports showed that intermittent dosing (MTD 9.4 mg/kg) on days 1 and 8 of a 21 day schedule was better tolerated than weekly dosing (MTD 3.2 mg/kg). In order to further understand the effects of dose and dosing frequency on tolerability we now report on the use of a once every 28 day schedule in a phase I study in cancer pts.
Methods: Pts with advanced solid tumors received GRN163L as a single agent at a dose of 9.4 mg/kg or 11.7 mg/kg IV over 2 hrs on day 1 of a 28 day cycle. A formal MTD was defined by dose-limiting toxicities during the first cycle. Telomerase activity was measured in blood mononuclear cells 24 hours after dosing as an exploratory end-point.
Results: As of June 15, 2010, 16 pts were treated (9.4 mg/kg, n = 3; 11.7 mg/kg, n = 13), with 11 pts evaluable. Median age was 65 yrs and median number of prior therapies was 4. Current status of patients is: 3 pts on study, 7 pts PD, 1 pt withdrawn due to toxicity. Of the 5 patients who received a 2nd cycle, 2 were delayed due to cytopenia. No significant toxicity was observed at 9.4 mg/kg. At 11.7 mg/kg, 2/8 pts developed neutropenia (grade 2, n = 1; grade 3, n = 1) and 7/8 pts developed thrombocytopenia (all grade 1). Nadirs were observed between 21 and 57 days after dosing at the higher dose. Related AEs included mild GI toxicity (nausea, vomiting, diarrhea, n = 1) and mild to moderate anorexia (n = 4). One pt had an infusion reaction resulting in withdrawal from the study. Due to hematologic toxicity and delayed dosing of C2, the maximum administered dose was 11.7 mg/kg. Although there was significant interindividual pharmacokinetic variability at this dose level, (Cmax, 190$\pm$69 ug/ml; AUC 1698$\pm$617 ug.hr/ml), this did not correlate with toxicity. Telomerase activity in leukocytes was inhibited by 33−72% in 3 pts studied to date.
Conclusions: GRN163L at a dose of 11.7 mg/kg given every 28 days is well tolerated, and results in excellent exposure and inhibition of telomerase activity in leukocytes. Further dose-escalation was considered undesirable due to cytopenias and the potential for delays in subsequent dosing. This alternate schedule remains an option for administration of GRN163L.

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A phase I study evaluating the pharmacokinetics (PK) and pharmacodynamic (PD) activity of the dual PI3K/mTor inhibitor GDC-0980 administered QW

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Background: The PI3K-AKT-mTOR signaling pathway is deregulated in a wide variety of cancers. GDC-0980 potently inhibits tumor growth of xenografts and has shown activity in preclinical models bearing PI3K mutant, PTEN-null, K-ras mutant, as well as PI3K pathway wild-type tumors in vitro and in vivo.
Methods: A phase I dose escalation study using a 3+3 design has been initiated in patients (pts) with advanced solid tumors or non-Hodgkin's lymphoma. Treatment is once weekly (QW) dosing with GDC-0980 in 4-week cycles. The objectives are to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD), evaluate PK and PD effects, and describe any observed anti-tumor activity of GDC-0980 on this schedule. PD assessments include pAKT levels in platelet-rich plasma (PRP), changes in pS6 in paired tumor biopsies, changes in FDG uptake via PET imaging, and changes in tumor vasculature via DCE-MRI. Archival tumor tissue is being evaluated for markers of PI3K pathway modulation.
Results: Seventeen pts have been enrolled in 4 successive cohorts of 6 to 50 mg GDC-0980 administered QW. GDC-0980 was generally well-tolerated with no Grade 3 or higher drug-related adverse events (AEs) or DLTs reported to date. The most common drug-related AEs reported to date include nausea, fatigue, lethargy, myalgia, vomiting, weight loss, pain, peripheral edema, stomatitis, and dry skin. Preliminary analyses of