**375** POSTER

**A Phase 1 dose escalation study of the oral heat shock protein 90 (Hsp90) inhibitor PF-04929113/SNX-5422 (PF-113) and its associated ocular toxicity**

J. Infante[1], G. Weiss[2], S. Jones[1], R. Tibes[2], J. Bendell[3], N. Brega[4], V. Torti[5], D. Von Hoff[6], H. Burris III[1], R. Ramanathan[2]. [1]*Sarah Cannon Research Institute, Drug Development Unit, Nashville TN, USA;* [2]*Virginia G. Piper Cancer Ctr/TGEN, Virginia G. Piper Cancer Ctr/TGEN, Scottsdale AZ, USA;* [3]*Sarah Cannon Research Insitute, Drug Development Unit, Nashville TN, USA;* [4]*Pfizer, Pfizer, Milan, Italy;* [5]*Pfizer, Pfizer, La Jolla CA, USA;* [6]*Virginia G. Piper Cancer Ctr/TGEN, Virginia G. Piper Cancer Ctr/TGENPfizer, Scottsdale AZ, USA*

**Introduction:** HSP90 regulates multiple chaperone proteins essential for cell growth and survival and inhibitors are actively being evaluated. PF-113 is a novel, oral, selective Hsp90 inhibitor prodrug, with preclinical anti-tumor activity in multiple tumor models. The objective of this study were to evaluate the safety and tolerability, determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD), and describe the pharmacokinetics (PK) and pharmacodynamics of PF-113 and its active moiety (PF-473) after oral administration in adult patients with advanced solid tumor malignancies and lymphoma.
**Methods:** This was a phase 1, open-label, dose-escalation study. Patients (pts) received PF-113 every-other-day (QOD) or once daily (QD) on a 3 week on/1 week off schedule. Doses ranged from 4 to 100 mg/m$^2$ for QOD and from 50 to 89 mg/m$^2$ for QD. Serial plasma concentrations of PF-113 and PF-473 were measured after the first dose and at steady state after 11 doses.
**Results:** Forty-four pts (26M/18F) were enrolled. Median age was 64. Treatment-related adverse events (AEs) were mainly low grade (G) and included diarrhea (47%), nausea (44%), and fatigue (30%). Reversible G 1−2 ocular symptoms of blurry vision and vision darkening were reported by 4 pts treated with 50 to 89 mg/m$^2$ QD. G 3 diarrhea was dose limiting in 2 of 3 pts at 89 mg/m$^2$. The MTD for the QD schedule was determined to be 67 mg/m$^2$, which was well-tolerated with manageable G 2 diarrhea (n = 3/7). One confirmed partial response (prostate) and stable disease (SD) in 6 pts with Her2 + breast, prostate, liver, neuroendocrine, GIST and small bowel carcinoid cancer have been noted.
Accrual to the study was halted due to the observation of visual symptoms prior to determining the MTD of the QOD schedule and further animal studies were conducted. PF-113 and its back up PF-847 were administered QD for 30 consecutive days to beagle dogs in order to assess structural and functional ocular changes. Functional changes were detected by electroretinography (ERG) as early as 4-days after dosing with PF-113. Retinal degeneration with a marked effect in the photoreceptor layer was observed with both compounds as early as 2-weeks to 30-days after the start of dosing.
**Conclusions:** Based on the clinical and preclinical safety observations, and despite the preliminary observation of antitumor activity, PF-113 has been withdrawn from clinical testing. Both PF-113 and its structurally different back-up compound show evidence of retinal toxicity by a yet unknown mechanism. These data indicate that HSP90 is a critical component of retinal function and that its prolonged inhibition can lead to irreversible retinal damage with photoreceptor death. Further evaluation is warranted to better understand whether this is a class/target mediated effect of HSP 90 inhibition.

**376** POSTER

**Preliminary results from a Phase 1 study of D-3263 HCl, a TRPM8 calcium channel agonist, in patients with advanced cancer**

A. Tolcher[1], A. Patnaik[1], K. Papadopoulos[1], T. Mays[1], T. Stephan[2], D.J. Humble[3], M.W. Frohlich[3], R.B. Sims[3]. [1]*South Texas Accelerated Research Therapeutics (START), Clinical Research, San Antonio TX, USA;* [2]*Dendreon Corporation, Research, Seattle WA, USA;* [3]*Dendreon Corporation, Clinical Affairs, Seattle WA, USA*

**Background:** D-3263 HCl is a calcium channel agonist that induces calcium influx and subsequent apoptosis in cells that express TRPM8. TRPM8 was originally discovered as a gene expressed in the prostate and upregulated in prostate cancer, and was subsequently identified as the cold-menthol receptor. D-3263 HCl, an orally administered small molecule agonist, showed evidence of activity in preclinical tumor models.
**Materials and Methods:** This open-label, Phase 1, dose escalation study was designed to assess the safety, tolerability, and pharmacokinetics of D-3263 HCl after a single oral dose (Day 1) and after repeat daily oral dosing (Days 8−28) in adult pts with advanced solid tumors refractory to standard therapy or for which no effective therapy is available. Pts without a dose limiting toxicity (DLT) or disease progression during the first treatment cycle were eligible for subsequent treatment cycles. Weekly safety monitoring, including cardiac and pulmonary testing, was conducted throughout each pts' participation in the study. The study was planned for 2 phases: a dose escalation phase to determine maximum tolerated dose (MTD), and an expansion cohort phase to study continuous daily dosing at the MTD.
**Summary of Results:** 15 pts were enrolled in the dose escalation phase: 3 pts at 50 mg/day, 7 at 100 mg/day, and 5 at 150 mg/day. The median age was 71 years, and 9/15 pts were male. The sites of primary cancers included prostate (8), colon (2), breast, lung, pancreas, leiomyosarcoma, and Kaposi's sarcoma (1 each). All pts had received at least 1 prior systemic therapy. The average maximum concentrations reached in the plasma (Cmax) for the 50, 100, and 150 mg cohorts was 3.3, 8.6, and 28.7 ng/mL, respectively, after a single oral dose. Total exposures (AUC) averaged 151, 550, and 1516 ng.hr/mL, respectively. The half life was >24 hrs for all dose groups. All pts experienced cold sensation, similar to menthol sensation, on skin and mucous membranes. Cold sensation was a DLT in 1 pt each at 100 mg/day and 150 mg/day. Troponin-T elevations were observed in 3 pts, including 1 DLT at 150 mg/day. There was no evidence of other cardiac abnormalities. The MTD was determined to be 100 mg/day, which is the dose under study in the expansion cohort. Three pts, all with advanced prostate cancer, had evidence of stable disease after 3 cycles, and 1 continues on study at 8+ cycles of therapy.
**Conclusions:** Pts in all dose cohorts experienced cold sensation, consistent with on-target activation of the cold-menthol receptor. Elevations in troponin-T were observed without other evidence of cardiac toxicity. The MTD was determined to be 100 mg/day. Men with advanced prostate cancer experienced preliminary results of disease stabilization. A more comprehensive review of the data from this dose escalation cohort will be presented.

**377** POSTER

**A phase 1, dose-escalation, safety, pharmacokinetic and pharmacodynamic study of PF-03732010, an IgG1 monoclonal antibody against P-cadherin (placental), administered to adult patients with advanced solid tumors**

Y. Bang[1], R. Cohen[2], T. Blumenkopf[3], Y. Zhang[3], M. Toh[3], A. Countouriotis[4], D. Shalinsky[4], S. Zhang[4], J. Gallo[5], J. Desai[6]. [1]*Seoul National University Hospital, Department of Internal Medicine, Seoul, Korea;* [2]*Fox Chase Cancer Center, Department of Medical Oncology, Philadelphia, USA;* [3]*Pfizer, Clinical Development-Oncology Business Unit, New London, USA;* [4]*Pfizer, Clinical Development-Oncology Business Unit, La Jolla, USA;* [5]*Pfizer, Clinical Development-Oncology Business Unit, Milan, Italy;* [6]*Royal Melbourne Hospital, Department of Medical Oncology, Melbourne, Australia*

**Background:** Cadherin isoform switching occurs during normal embryonal development and is often associated with tumor progression and the epithelial–mesenchymal transition. P-cadherin (P-cad) is often overexpressed in tumor cells whereas normal cells scarcely express P-cad. PF-03732010 (PF) is a fully human anti-P-cad, IgG1 mAb with high affinity ($K_d$ = 2.53 nM) and selectivity (>100× over E-cad; negative for N-cad) for its target. PF causes tumor growth inhibition in various xenograft models.
**Methods:** Patients (pts) with advanced solid tumors and P-cad overexpression as assessed by IHC at a central lab, were enrolled in a phase 1 study with a standard 3 + 3 design. Single agent PF was initially administered biweekly (bw). After observing a terminal half life (t1/2) of ~ 96 hours, PF was given on a weekly (w) schedule. Pharmacokinetic (PK) samples were collected. Functional imaging with FLT PET was used as a pharmacodynamic surrogate and was assessed at baseline and at Cycle 3 during the study. Tumor response was assessed at baseline and every 8 weeks thereafter by RECIST v1.0.
**Results:** So far, 37 pts have been treated with PF across 6 bw dose levels (0.5 to 15 mg/kg), and across 3 w dose levels (4 to 15 mg/kg). Median age was 60.1 years and median ECOG PS was 1. The most frequent tumor types included were CRC (24 pts), gastric cancer (4 pts), and breast cancer (3 pts). The 15 mg/kg w dose is the maximum feasible dose (MFD) and this dose level is being expanded to 12 pts (7 pts enrolled so far). Up to 19 May 2010, PF has been well tolerated. G3−4 treatment-related AEs have included G4 lipase (1 pt at 8 mg/kg bw) considered a DLT, and G3 proteinuria and acute renal failure (1 pt at 15 mg/kg bw, also DLTs). Preliminary PK analysis shows the estimated t1/2 and clearance for the MFD are similar to the other cohorts, with median values (all cohorts) ranging from 69.3 to 140 hours and 0.305 to 0.541 ml/hr/kg, respectively. Median Tmax ranges from 1.5 hours to 3.5 hours, the Vss from 37 to 79.4 ml/Kg while the median Cmax achieved in the MFD cohort was 305,000 ng/ml. Hierarchical modeling of FLT-PET results demonstrated a significant decrease in SUV during dose escalation. No objective responses have been observed so far. Three pts (2 CRC and 1 bladder carcinoma) have been on treatment for ⩾ 6 months.
**Conclusions:** In this phase 1 study, PF has been generally well tolerated up to a dose of 15 mg/kg w and further characterization of this dose level is in progress.