plasma VEGF concentrations, decreases tumor microvessel density, and substantially slows tumor growth. When given together with cytotoxic agents or with bevacizumab, PTC299 enhances tumor growth delay.
Methods and Materials: This Phase 1 randomized, double-blind, placebo-controlled, escalating single-dose study in healthy adult volunteers includes 2 stages with dose finding performed in Stage 1 and food effects evaluated in Stage 2. To determine PTC299 safety, PK, and effects on plasma VEGF levels, subjects are followed with clinical observations, safety laboratory testing, and frequent plasma sampling.
Results: 8 subjects (4 males, 4 females; 6 PTC299, 2 placebo) have been enrolled at each of 4 progressively higher dose levels, for a total of 32 subjects with median age [range] of 45 [23−55] years. PTC299 has been well tolerated with no serious, dose-limiting, or definitively drug-related adverse events. PK data indicate dose-proportional increases in plasma exposures. Target trough plasma concentrations ($\geqslant$0.1 μg/mL) active in xenograft models have been exceeded for $\geqslant$12 hours at doses $\geqslant$0.3 mg/kg, supporting the potential for dosing once or twice per day. The PK data are well-described by a 2-compartment model. Further accrual is ongoing.
Conclusions: PTC299 is the first drug specifically designed to modulate post-transcriptional control mechanisms to treat human disease. In this initial clinical study, PTC299 shows safety at plasma exposures associated with preclinical activity. Final data on dose ranging, safety, PK, food effects, and plasma VEGF levels will be presented at the meeting. PK modeling will be used to project an appropriate dosing regimen for subsequent multiple-dose studies in cancer patients.

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Preclinical development of PTC299: an orally bioavailable small molecule drug that selectively inhibits the production of VEGF protein, tumor growth, and microvessel density

T. Davis, L. Cao, N. Tamilarasu, N. Risher, H. Qi, C. Romfo, J. Bombard, J. Sheedy, M. Weetall, Y. Moon. *PTC Therapeutics, South Plainfield, NJ, USA*

Background: We developed a phenotypic high-throughput screening platform, termed GEMS (Gene Expression Modulation by Small molecules), to identify small molecules that modulate gene expression by targeting processes controlled by the untranslated regions (UTRs) of the mRNA (*e.g.* message stability and translation initiation). This platform was utilized to identify molecules that inhibit the production of vascular endothelial growth factor A (VEGF). Following an extensive analoging campaign PTC299 was synthesized, evaluated biologically and pharmaceutically, and developed as an antiangiogenic agent for use in cancer and other pathologies with aberrant angiogenesis.
Materials and Methods: A high throughput screen was conducted using cells stably expressing a reporter gene under the control of UTRs from the VEGF mRNA. Hits that reduced the expression of the reporter were confirmed and SAR was driven by measuring inhibition of hypoxia-induced VEGF production in cells. VEGF protein was measured by ELISA.
Results: PTC299 inhibits the expression of all major isoforms of VEGF-A in cell culture across a wide variety of tumor types, with EC50 values in the low nanomolar range, and is highly selective for inhibition of VEGF expression when compared to a number of other growth factors, cytokines, and intracellular proteins. Results from mechanism of action studies suggest that PTC299 acts by inhibiting the 5′ UTR-dependent translation of the VEGF protein. In xenograft-bearing animals treated with PTC299 there was a marked reduction of intratumor and circulating hVEGF (up to 90%) and a normalization of tumor vasculature within a matter of days. With continued dosing of PTC299, the reduction in VEGF correlated with a significant reduction in tumor growth in a number of subcutaneous and orthotopic xenograft models, including colorectal, NSCLC, breast, fibrosarcoma and neuroblastoma. PTC299 also demonstrated additive or synergistic activity in combination with a number of standard-of-care cytotoxics, including taxol, doxorubicin and CPT-11. PTC299, with a therapeutic window of >30, was well-tolerated in IND-enabling toxicology studies that included multiday dosing in rats and dogs.
Conclusions: PTC299 is effective in reducing the production VEGF and controlling tumor growth in a number of model systems. IND-enabling toxicology studies have demonstrated a sufficient safety window and a dose-ranging Phase I clinical trial in healthy volunteers was initiated in April, 2006.

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A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab (Avastin®) in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride (Tarceva®) compared with chemotherapy alone for treatment of recurrent or refractory non–small cell lung cancer

R. Herbst[1], V. O'Neill[2], L. Fehrenbacher[3], C. Belani[4], P. Bonomi[5], L. Hart[6], O. Melnyk[7], A. Sandler[8], M. Lin[2], J. Bloss[2]. [1]*The University of Texas M. D. Anderson Cancer Cent, Thoracic/Head and Neck Medical Oncology, Houston, TX, USA;* [2]*Genentech, Inc., South San Francisco, CA, USA;* [3]*Kaiser Permanente Northern CA, Vallejo, CA, USA;* [4]*University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA;* [5]*Rush-Presbyterian-St. Lukes Medical Center, Chicago, IL, USA;* [6]*Florida Cancer Specialists, Ft. Myers, FL, USA;* [7]*Bay Area Cancer Research Group, LLC, Concord, CA, USA;* [8]*Vanderbilt University Medical School, Nashville, TN, USA*

Background: Bevacizumab (B) is a recombinant, humanized anti-VEGF MAb. Erlotinib (E) is a potent, reversible, highly selective and orally available EGFR tyrosine-kinase inhibitor. Both compounds have demonstrated a survival benefit in the treatment of non-small cell lung cancer (NSCLC): bevacizumab when added to chemotherapy in the first line setting, and erlotinib when given alone in the 2nd/3rd line. In addition, a single arm phase I/II study of the combination of bevacizumab and erlotinib has shown encouraging survival and response rate data, with a favorable safety profile (Herbst et al, JCO 2005).
Methods: A multicenter, randomized phase II trial was conducted to evaluate the safety of combining bevacizumab with chemotherapy (docetaxel or pemetrexed), or with erlotinib; and to make a preliminary assessment of the efficacy of combining bevacizumab with chemotherapy or erlotinib relative to chemotherapy alone, as measured by progression-free survival. All patients had histologically confirmed non-squamous NSCLC and had experienced disease progression (clinical or radiographic) during or following one platinum-based regimen for advanced stage disease. Randomization was on a 1:1:1 basis to docetaxel or pemetrexed plus placebo v docetaxel or pemetrexed plus bevacizumab v bevacizumab plus erlotinib. Patients remained in the treatment phase of the study until documented radiographic or clinical disease progression or through 52 weeks of study treatment.
Results: Between August 2004 and November 2005, 120 patients were randomized and treated.

	Chemotherapy (n = 41)	Chemotherapy +B (n = 40)	B+E (n = 39)
Median PFS, mo	3.0	4.8	4.4
Adjusted Hazard Ratio (95% CI)	NA	0.66 (0.38, 1.16)	0.72 (0.42, 1.23)
Overall Survival, 6-month rate (%)	62.4	72.1	78.3
Response rate, n (%), CR/PR	5 (12.2)	5 (12.5)	7 (17.9)
Drug discontinuation due to AE, n (%)	10 (24.4)	10 (25.0)	4 (10.3)
SAEs, n (%)	22 (53.7)	16 (40.0)	13 (33.3)
Grade 5 drug-related AEs, n (%)	2 (4.9)	3 (7.5)	1 (2.6)
Grade 3–5 pulmonary hemorrhage	0	2(5)	1 (2.6)

Conclusions: The observed data favor the addition of bevacizumab to either chemotherapy or erlotinib over chemotherapy alone. No new or unexpected safety signals were noted. The toxicity profile of the bevacizumab-erlotinib combination is favorable when compared to either chemotherapy-containing group. The bevacizumab-erlotinib combination may represent an alternative to chemotherapy-based treatment in this setting. Updated OS data will be presented.

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Changes in computed tomography perfusion scan parameters and circulating endothelial cells following bevacizumab administration in patients with advanced hepatocellular carcinoma

A. Zhu[1], N. Holalkere[1], A. Norden-Zfoni[2], A. Muzikansky[1], J. Heymach[3], D. Sahani[1]. [1]*Massachusetts General Hospital, Harvard Medical School, Boston, USA;* [2]*Children's Hospital, Harvard Medical School, Boston, USA;* [3]*M.D. Anderson Cancer Center, Houston, USA*

Purpose: Hepatocellular carcinoma (HCC) is a highly vascular tumor with a poor prognosis. In a phase II study using bevacizumab (B) combined with gemcitabine and oxaliplatin (GEMOX) in advanced HCC, we examined changes in computed tomography (CT) perfusion scan parameters and circulating endothelial cells (CECs) as surrogate angiogenesis markers following B administration.