



Tower Cancer Research Foundation

The Frank E. Rosenfelt Drug Development Program

Hope, Healing and Humanity Hope, Healing and Humanity Hope, Healing and Humanity Hope, Healing and Humanity Hope, Healing and Humanity

Phase I & II Clinical Trials from Tower - July 2009

Dear Colleagues:

Once again, I wish to update you on the status of selected Phase I/II clinical trials at Tower Cancer Research Foundation (TCRF). Also, you can find a full description of all Foundation activities and clinical trials, our staff, and also educational publications on our new updated website at www.towercancerfoundation.org.

Again, I encourage you to contact us by phone or e-mail to discuss any potential patients under consideration for the trials outlined below. I can be reached at 310-285-7206 or by e-mail at rosenp@toweroncology.com. Dr. Peter Lee, TCRF Associate Medical Director, can be reached at 310-205-5787 and his e-mail is leep@toweroncology.com. Marie Fuerst RN our Research Nursing Director also can be reached at 310-285-7269 or at the following e-mail: fuerstm@toweroncology.com. We all look forward to working with you in the future.

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Multiple PRIMARY SITES:

AMG 208: Phase I, first in human trial, of an oral c-Met inhibitor. Trial will consist of two phases: a dose finding phase open to all tumor types and an expansion phase focusing on colorectal, gastric, pancreatic, hepatocellular and renal carcinomas; tumors in which overexpression of c-Met is common. For the dose finding part of the trial, evaluable (not necessarily measurable) disease will qualify whereas for the expansion phase measurable (RECIST criteria) disease is required. ECOG 0-2. Creatinine <2.0 mg%. CrCL >60 ml/min. Plt. >100K and ANC >1,500 /mm³.

CI-CPI-613-02: First in human trial. Novel mechanism of action taking advantage of abnormal glycolysis in tumors. IV infusion twice weekly; three weeks out of 4. Minimal toxicity in animal models. All solid tumors including lymphomas. KPS > 70. Ejection Fraction >35%. No restriction on number of prior therapies.

PRLX9396: Phase I first in human trial of an agent with striking preclinical activity initially thought to be a ras inhibitor. All solid tumors including sarcoma are eligible. No restrictions on prior therapies. Nearing maximal dose with side effects to date including mild leukopenia, thrombocytopenia, and febrile reactions.

PHA 739358: Phase Ib trial of an aurora kinase inhibitor (antimitotic). Drug combined with gemcitabine, docetaxel, avastin, or carboplatin. Open for all solid tumors including sarcoma and lymphoma. ECOG 0-1. Drug has hematological toxicity. Must have had <7 cycles of alkylating agent. May have received the chemotherapy or avastin partners previously.

PX-171-007 (carfilzomib) : PX-171-007 (carfilzomib): This Phase Ib/II trial is being reopened with a prolongation of drug infusion time (30 minutes) and increased dosing based upon the

favorable results noted in the original trial. The Phase Ib portion of the trial (dose escalation) is available to patients with all pre-treated solid tumors as well as myeloma. When the MTD is reached a Phase II portion will be conducted focusing on renal cell carcinoma as well as small cell and non-small cell lung cancers, and untreated myeloma. Based on data that becomes available, other tumor types may be accepted as well. Despite being a proteasome inhibitor, the drug is essentially devoid of neurotoxicity. Entrance criteria are liberal with a CrCl >20 ml/min. ECOG 0-2.

COLORECTAL

AMG 20060579: This is a Phase II randomized trial for patients with metastatic colorectal cancer who have mutant k-ras and who have progressed after a FOLFOX-like regimen with or without avastin. Patients will be randomized between AMG 655, a Death Receptor agonist, AMG 479, an insulin growth factor receptor-1 antibody (IGFR-1) and placebo. Patients with mutant k-ras will not benefit from EGFR inhibition and this trial attempts to examine other pathways that might be exploited.

LYMPHOMA:

Bendamustine-Rituxan: Phase II trial of these agents in relapsed/refractory diffuse large B cell lymphoma. ECOG =/ <2, platelets >75,000, ANC >1000, Cr <2.0, or CrCl >50. Prior auto stem cell transplant allowed.

CC-5013-MCL-001 (EMERGE TRIAL): Phase II trial of lenalidomide (Revlimid) for patients with mantle cell lymphoma who have had prior exposure to an anthracycline, cyclophosphamide, rituximab and bortezomib (Velcade®). Must have cyclin D1 overexpression by IHC or t(11;14) by FISH. (Rare cyclin D2 or 3 overexpression accepted). ECOG 0-2. ANC >1500/mm³; Platelets >60K, CrCl >30 ml/min. Patients with neuropathy accepted.

Pralatrexate: This is a Phase II trial of a novel antifol with unique properties (see below) in aggressive B cell malignancies including Diffuse Large B Cell Lymphoma, Mediastinal Large B-Cell Lymphoma, Transformed Follicular Lymphoma, Grade 3 Follicular Lymphoma, and Mantle Cell Lymphoma. Up to three prior therapies allowed. ECOG 0-2. CrCl >50 ml/min. Will be pretreated with vitamin B12 and folic acid.

MYELOMA

PX-171-03/04 (carfilzomib): These two complementary phase II trials focus on myeloma where this agent has demonstrated significant activity in prior studies. These trials will look at bortezomib-naïve and bortezomib-exposed patients respectively. Patients must have M protein spikes in serum and/or urine and a creatinine clearance >30 ml/min. Drug has demonstrated early infusion reactions which are pretreated with steroids during first cycle. No significant neuropathy.

PANCREAS CANCER:

CA046: A phase III randomized trial for front-line metastatic disease of gemcitabine vs. the combination of gemcitabine and abraxane (ABI-007). This critical trial is based upon very encouraging Phase I/II data obtained by Dan von Hoff and presented at AACR and ASCO

GI 4000: Randomized Phase II trial. For patients who have undergone a R0/R1 resection of ductal carcinoma of the pancreas. Involves the sequencing of the ras gene from archival tissue and manufacturing a yeast derived vaccine. Trial randomizes these patients between gemcitabine and vaccine vs. gemcitabine and an incomplete vaccine. ECOG 0-2. Gemcitabine may be administered locally by patient's oncologist. Rapid referral after (or even before) surgery to assure that the time frame for enrollment is adequate.

Pralatrexate

We are opening a trial of pralatrexate for patients with relapsed/refractory aggressive B cell tumors. Pralatrexate is a novel antifolate which has demonstrated significant activity in a variety of T cell lymphomas with activity approaching 50%. The drug has not been adequately studied in B cell lymphomas. Although it belongs to an old class of antitumor agents, the antifolates, pralatrexate has significantly enhanced antitumor activity based upon more effective intracellular internalization by the 1-carbon reduced folate carrier (RFC-1), a fetal oncoprotein expressed in fetal and malignant tissue. Following internalization, binding to the target, DHFR (dihydrofolate reductase) is enhanced by increased polyglutamation. Its toxicities (hematological and mucositis) are mitigated by medication with vitamin B12 and folic acid.

Update on Carfilzomib (PX-117-007):

The initial results of this trial of the proteasome inhibitor, carfilzomib, in solid tumors led to an oral presentation that I presented at ASCO. The trial was encouraging in that signs of activity of carfilzomib as a single agent were observed in patients with renal cell carcinoma, small cell and non-small cell lung cancer. Such activity had not been observed with bortezomib (Velcade) the only approved proteasome inhibitor. As a result of this activity, the trial is reopening as a Ib/II study attempting to exploit this preliminary activity by lengthening the time of infusion to 30 minutes and by increasing the dose. There will be a dose escalation phase available to patients with any pre-treated solid tumor. When the maximum tolerated dose has been achieved, the Phase II will focus on renal cell carcinoma, small cell and non-small cell lung cancer. Please note that carfilzomib has demonstrable activity in myeloma and that we have two trials available focusing on bortezomib-naïve and bortezomib-exposed patients.

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