



Tower Cancer Research Foundation

Hope, Healing and Humanity

Trials For Relapsing/Refractory Cancer Patients- September 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.

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 requiring tylenol prophylaxis.

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 same chemotherapy 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.

CLL

BCX1777-210 (Forodesine): Phase II trial for patients with CLL of a purine nucleoside phosphorylase (PNP) inhibitor. Shows activity in T cell disease and is being studied in B-CLL at a higher oral bid dosing schedule. Preliminary antitumor activity. CLL patients with either Rai 3 or 4 disease or symptoms requiring therapy. Primary resistant (no CR or PR) or PD after response to at least one prior regimen. Or treatment naïve subjects who meet one of the following: a) age >65, b) ECOG 2 or 3, c) inability to tolerate standard cytotoxic therapy in the physician's opinion. Over all ECOG 0-2. Cr <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.

Hepatocellular carcinoma

M10-963: Phase III randomized trial comparing sorafenib with ABT-869, an oral kinase inhibitor in Child-Pugh Class A HCC. ABT-869 is an effective inhibitor of all three VEGF receptors and PDGF. Trials in HCC to date suggest a possible OS advantage over sorafenib. Patients must have unresectable or metastatic disease. Must have measurable disease. ECOG 0-1. Child-Pugh A. Bili <3, AST/ALT <5X ULN, INR <1.5, Platelets >50,000 (75,000 if spleen not enlarged). No prior systemic therapy for HCC but local therapies allowed. EF>50%. Blood pressure controlled.

LUNG CANCER:

A808107/105: A Phase III Randomized Open-label Trial of PF-02341066 vs.pemetrexed or docetaxel in patients with advanced NSCLC with a mutant ALK gene locus. This involves a novel agent (see below) targeted against a mutant ALK protein in NSCLC. It is an oral agent; well tolerated. One prior line of platinum-containing chemotherapy (metastatic, adjuvant, neoadjuvant). May have received erlotinib/gefitinib. Controlled brain metastases accepted. ECOG 0-2. The 105 study will accept progressions on the randomized trial who received chemotherapy with pemetrexed or docetaxel (former preferred). Other exceptions can be discussed individually. This study is open-label and non-randomized. See below for discussion.

LYMPHOMA:

155-CL-031 (YM155); Phase II trial of YM 155, a survivin antagonist plus rituximab in previously treated patients with CD20-positive B cell lymphomas who are ineligible for or have previously received an autologous stem cell transplant. Patients should have transformed or primary diffuse large B cell lymphoma, grade 3 follicular lymphoma, or mantle cell lymphoma. At least one but no more than 3 prior regimens, including one anthracycline-based regimen. Must have had at least a PR >6 months following last treatment regimen. ECOG 0-1. Platelets >100,000. CrCl >60

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

CC-5013-TCL-001 (Revlimid): A Phase II trial of lenalidomide in patients with relapsed/refractory T-cell lymphoma. May have PTCL or MF. Must have had at least one prior systemic combination therapy with no limit on number of agents/trials. May have had an autotransplant. ECOG 0-2. ANC >1500 and platelets $>60,000$. CrCl >60 . Not planning stem cell transplant.

C14004 (MLN8237): Phase II trial of an oral aurora kinase A inhibitor in aggressive NHL. Includes Diffuse Large B Cell Lymphoma, mantle cell lymphoma, transformed follicular lymphoma ($>50\%$ large cells), Burkitt's lymphoma, Peripheral T cell lymphoma and B-Lymphoblastic lymphoma-leukemia. Oral agent. ECOG 0-2. Prior autologous stem cell transplant must have occurred more than 6 months before enrollment and allotransplants are not 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 $>1500/mm^3$; 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.

SNDX 275-0501 (Entinostat): A Phase II trial of a novel histone deacetylase inhibitor for patients with relapsed/refractory Hodgkin lymphoma. Patients must have either been through an autologous stem cell transplant or be ineligible. They may have had an allotransplant if they are off immune suppression. ECOG 0-1 (negotiable). Platelets $>25,000$. Measurable disease. We are only site open in a large geographical area with this drug which has shown preliminary activity in HL. The drug is oral and is given twice a month, a very favorable schedule. Patients with borderline eligibility issues may be discussed.

Myeloproliferative Diseases

INCB 18414-351: Phase III randomized-placebo controlled trial of JAK2 inhibitor (INCB018424), an oral agent in patients with primary myelofibrosis, or myelofibrosis secondary to polycythemia vera or essential thrombocythemia. Phase II data encouraging. Patient need not have JAK2 mutation. May be previously treated or untreated but off therapy. Spleen must be 5 cm. below the left costal margin and platelets must be $>100,000$ (in absence of myelotoxic agents). Some symptomatology is required which should be discussed on an individual basis. Cross-over to active drug allowed as early as 4 weeks under some circumstances. See below for discussion.

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.

TREATMENT FOR MYELOFIBROSIS

We have activated the INCB 18414-351 Trial for patients with Myelofibrosis, either primary or secondary to PV or ET. This JAK 2 inhibitor has already demonstrated very encouraging results in PV, ET and Myelofibrosis and this is the definitive randomized trial. Patients need not demonstrate JAK2 mutations. They may have been treated with other agents or be treatment naïve. To qualify the spleen must extend at least 5 cm beneath the left costal margin and the baseline platelet count must be >100,000 (off myelotoxic agents). There must be some symptomatology which will be discussed on an individual basis. The drug itself has been well-tolerated with myelosuppression the main side effect. Patients on placebo may cross-over after unblinding as early as 4 weeks after onset of therapy if they meet certain criteria.

NSCLC With Mutant ALK Gene

PF-02341066 is an oral tyrosine kinase inhibitor targeting a novel EML4-ALK fusion gene found in roughly 5% of the population with NSCLC. These patients appear to have adenocarcinomas, are usually non-smokers and are often younger than the usual age of lung cancer. The mutation is discovered using a FISH assay. Patients may sign consent for screening for the mutation even during their primary therapy. Those patients with the mutation had a 62% response rate similar to patients receiving EGFR based TKI therapy with mutations. This represents another major step in true personalized therapy though it applies to a minority of patients who can be readily identified.

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