



Tower Cancer Research Foundation

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

Trials For Relapsing/Refractory Cancer Patients- March 2010

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 website at www.towercancerfoundation.org.

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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VARIOUS 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, CrCl >60, Plt. >100,000, 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 1b trial of an aurora kinase inhibitor (antimitotic). Drug is combined with gemcitabine. Open for all solid tumors including sarcomas and lymphomas. ECOG 0-1. Drug has hematological toxicity. Must have had <7 cycles of an alkylating agent. May have received gemcitabine 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. ECOG 0-2.

BREAST

CTK1258A2202: A multi-center, open label Phase II trial of the tyrosine kinase inhibitor TKI258 in FGFR1 amplified and non-amplified metastatic HER-2 negative breast cancer. TKI258 (see below) is a tyrosine kinase inhibitor directed against FGFR1. In this trial four cohorts of patients will be studied: 1) FEGFR1 pos. ER pos; 2) FGFR1 pos ER neg; 3) FGFR1 neg ER pos; 4) FGFR1 neg ER neg. ER pos patients must have received at least one hormonal therapy and no more than three prior lines of chemotherapy for metastatic disease. ER neg patients must have received at least one prior line of chemotherapy and no more than three. Although the drug is being developed with FGFR1 as a target, there may be benefit for patients without FRGFR1 amplification.

COLORECTAL

AMG20060579: 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 oral agent which appears well tolerated. Results in Phase I trials showed that over 60% of patients with mutations responded. One prior line of platinum-containing chemotherapy (meta- static, adjuvant, neoadjuvant). May have received erlotinib/gefitinib. Controlled brain metastases accepted. ECOG 0-2. We are able to accept tissue specimens to screen for the mutant ALK protein found in about 5% of patients. The 105 study will accept progressions on the randomized trial who received chemotherapy with pemetrexed or docetaxel (former preferred). Other ex- ceptions can be discussed individually. This study is open-label and non-randomized.

E7389-0000-205: Phase II multi-center, randomized study of two different dose regimens of eribulin mesylate in combination with intermittent erlotinib in patients with previously treated advanced non-small cell lung cancer. Have received at least one platinum containing doublet for recurrent or advanced disease with disease progression during or after last regimen. ECOG 0-2. Measurable disease. Creatinine < 2 mg% (CrCl >40). No prior erlotinib. Examining two schedules of eribulin, an antimitotic non-taxane, non-vinca agent with no cross-reactivity with those agents.

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 0-2, platelets >75,000, ANC>1000, Cr <2.0, or CrCl>50. Prior auto stem cell transplant allowed.

C14004: Phase II trial of an oral aurora kinase A inhibitor MLN8237 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, Platelets >60K, CrCl >30 ml/min. Patients with neuropathy accepted.

C16002: Phase I trial of a second generation proteasome inhibitor, MLN9708, with preclinical evidence of enhanced antilymphoma activity. Open for all types of NHL and Hodgkin lymphoma with the exception of Waldenstrom's disease. CLL allowed. ECOG 0-2. Measurable disease. No limit on number of lines of prior therapy. ANC >1250 and platelets > 100,000. CrCl > 30. Peripheral neuropathy cannot exceed grade 2. Autologous stem cell transplant > 6 months before. IV weekly schedule.

Pralatrexate: This is a broad Phase II trial of a novel antifol with enhanced cellular uptake and retention. The trial has been broadened to encompass a large proportion of B-cell NHL, essentially all histological types including indolent disease. ECOG 0-2> CrCl >50. Require pretreatment with vitamin B 12 and folic acid. This agent recently approved for peripheral T cell lymphoma.

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.

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.

Prostate Cancer

COU-AA-015: A Phase I trial of abiraterone acetate plus prednisone in a drug-drug interaction study with dextromethorphan and theophylline. Abiraterone appears to have promising activity in castrate resistant prostate cancer. The study is designed to test any potential C450 interactions of importance. It is open to patients who are

castrate resistant. They may be chemotherapy naïve and may have received ketoconazole, expanding the entry criteria.

MDV3100: an oral pure, highly potent androgen receptor antagonist developed by Charles Sawyers. In this randomized Phase III, double-blind placebo controlled trial, patients with advanced prostate cancer with castrate levels of serum testosterone and prior therapy with taxotere will be eligible. The randomization will be 2:1 favoring the study agent. Patients will be allowed low doses of steroids (prednisone 10 mg/day). They may have had no more than 2 prior chemotherapy agents. In general prior ketoconazole is disallowed. To be eligible, patients must have progressive disease by PSA, bone or soft tissue disease (at least one).

Urothelial Cancer

BI 6727: an IV Polo-like kinase 1 inhibitor (see below). Phase II, nonrandomized trial. Patients must have received prior neoadjuvant, adjuvant or front-line chemotherapy. Must have measurable disease. ECOG 0-2. Primary may be bladder, renal pelvis, ureter, urethra, etc. No more than one prior chemotherapy regimen. Serum creatinine < 1.5. Drug has shown some myelosuppression. Active in urothelial malignancy in Phase I trial.

Featured New Agents

An Inhibitor of FGFR1 (Fibroblast Growth Factor 1)

In the continuing search for agents that may hit a “druggable target”, a trial has opened featuring TKI 1258, a kinase inhibitor of FGFR 1. FGFR 1 is amplified in about 10% of breast cancers and preliminary studies reveal evidence of antitumor activity in these situations. This trial will involve screening archival tissue for FGFR amplification but the study will not be restricted to patients with that alteration since there may be evidence of benefit for patients without amplification. (see above).

A New Proteasome Inhibitor for Lymphoma

Velcade (bortezomib), the only approved proteasome inhibitor, is licensed for treatment of myeloma and mantle cell lymphoma. Clinical activity has also been seen in follicular lymphoma, Waldenstroms macroglobulinemia, and possibly other lymphoma types. MLN 9708 is a proteasome inhibitor that belongs to the same class as bortezomib (a diboronic proteasome inhibitor). However, preclinical studies suggest significantly enhanced activity in a variety of NHL. Thus we have opened a Phase I trial of this compound in a broad variety of NHL as well as HL. (see above)