



Trials For Relapsing/Refractory Cancer Patients- December 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 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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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, 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 Ib trial of an aurora kinase inhibitor (antimitotic). Drug is combined with gemcitabine, docetaxel, 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. 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

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 exceptions can be discussed individually. This study is open-label and non-randomized.

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.

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, Platelets >60K, CrCl >30 ml/min. Patients with neuropathy accepted.

Pralatrexate: This is a Phase II trial of a novel antifol with unique properties 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. Will be pretreated with vitamin B12 and folic acid. This agent also has been FDA approved in 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.

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.

MYELOMA

PX-171-04 (carfilzomib): Carfilzomib is a novel proteasome inhibitor with known activity in multiple myeloma and almost no neurotoxicity, therefore making it a reasonable alternative to bortezomib. Patients for this trial must be bortezomib-naïve. They must have M protein spikes measurable in serum and/or urine. CrCl must be >30 ml/min. Drug has demonstrated early infusion reactions, which are alleviated by dexamethasone in first-cycle.

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

MDV3100 (see below): 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

MDV 3100: This is a novel small molecule androgen receptor antagonist which has several unique properties differentiating it from older antiandrogens such as bicalutamide including more tight binding to the androgen receptor while inhibiting translocation of the receptor to the nucleus and subsequent DNA binding. Furthermore there is agonistic activity seen in the first generation antiandrogens but not seen with this agent. . This drug is expected to have activity in so-called castration resistant prostate cancer, in that many of those cases still continue to overexpress the androgen receptor and may respond to a potent pure androgen antagonist.

BI 6727: This is an agent which inhibits the so-called Polo-like kinase -1 (Plk-1), one of a family of kinases intimately involved in normal mitosis. The drug is being developed in several malignancies including urothelial tumors where it was found to be active in phase I trials. The drug has been well tolerated although there is potential for myelosuppression.

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