

Phase I Clinical Trials Program

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Recent scientific breakthroughs have improved our understanding of cancer biology and yielded an increasing number of attractive molecular targets for therapy. Many of these targeted therapies offer the promise of improved efficacy with fewer side effects compared to existing cancer therapeutics. The phase I program at Fox Chase provides the gateway for new compounds to enter the institution from private industry and the National Cancer Institute. With each new agent, the program seeks to catalyze collaborations with in-house and extramural basic scientists to investigate further the mechanism of action of these agents as well as to seek biomarkers of drug effect based on blood tests or tumor biopsies. Over the past year more than 200 patients have been enrolled in phase I trials at Fox Chase Cancer Center.



Small Molecule Therapeutics

The phase I program is collaborating in the testing of a variety of small molecules, most of them inhibitors of growth factor pathways or enzymes involved in mitosis. The Aurora protein kinases, for example, are key components in the regulation of centrosome and spindle function as well as chromosome segregation in early mitosis. Aurora A and aurora B are over-expressed in a variety of solid tumors. Preclinical studies demonstrate that interruption of aurora kinase function has significant anti-cancer effects. We are currently participating in two phase I dose escalation studies of aurora kinase inhibitors. One of these is an inhibitor of Aurora A and B whereas the 2nd is more selective for Aurora A.

MEK is a critical enzyme in the MAP kinase signal transduction pathway, communicating growth signals to cancer cells via receptor tyrosine kinases that include EGFR, IGF-1R and PDGFR. Cell signaling through these receptors is essential in cell survival, proliferation, and differentiation. Small molecule inhibi-

tors of MEK have been shown to inhibit tumor cell growth in various animal models. We are evaluating a potent MEK inhibitor administered twice daily by mouth in a study that includes assessments of multiple biomarkers of drug effect on skin, hair follicles, and tumor.

Recent clinical trials data and FDA approvals of inhibitors of the EGFR family of growth factor receptors validates their importance in the growth of solid tumors. Many patients do not respond to or eventually become resistant to the available agents, however, suggesting an opportunity to develop agents that target this pathway via a different mechanism. Sheddase is an enzyme responsible for the cleavage of the extracellular domain of HER2 that results in constitutively active HER2 signaling. Sheddase also cleaves EGFR ligands that bind and activate EGF receptors. We are conducting a dose escalation phase I trial of a novel oral sheddase inhibitor, which may ultimately have potential widespread use for a variety of solid tumors.

Monoclonal Antibody Therapeutics

Antibodies have been a long-standing component of the phase I program. We are continuing to collaborate in trials of antibodies that target the TRAIL death receptors. We have completed phase I studies of HGS-ETR1, a fully human monoclonal antibody to the TRAIL-R1 receptor, in subjects with advanced solid cancers and lymphomas. At this time we are continuing evaluation of that antibody in combination with chemotherapy for solid tumors. Recently, we have initiated similar studies of HGS-ETR2, which targets the TRAIL-R2 receptor, in combination with various commonly used solid tumor chemotherapy regimens.

Other antibody studies include a phase I dose escalation study of a humanized monoclonal antibody that is an agonist for the lymphotoxin beta receptor, which is another member of the tumor necrosis factor receptor superfamily and mediates tumor cell apoptosis. A phase I dose escalation study of a humanized antibody directed against the VEGFR-2 receptor is ongoing; targeting of the receptor rather than the ligand of the VEGF axis may extend the scope of angiogenesis inhibition. Antibodies can also

serve to deliver cytotoxic agents to tumor tissues or enhance anti-tumor immunologic responses. Thus, we are evaluating an immunoconjugate consisting of a monoclonal antibody targeting the Lewis-Y antigen, which is expressed on a variety of solid tumors. This antibody is linked to calicheamicin, a potent antibiotic which exerts its antitumor effects by binding to the minor groove of DNA resulting in double-strand breaks. A second study is assessing a monoclonal antibody targeting the Epithelial Cell Adhesion Molecule (EpCAM) linked to interleukin-2 with the goal of targeting and delivering IL-2 to the tumor, in order to enhance tumor-specific cytotoxic T cells.

In summary, we continue to offer a broad range of novel agents with unique mechanisms of action as part of the international effort to turn recent discoveries in biology into the next generation of cancer therapies. Nearly a third of the trials in our phase I program are first-in-human studies. They represent collaborations with pharmaceutical sponsors, the National Cancer Institute, as well as peer cancer centers in the U.S. and abroad.

Publications

Cohen, S.J., Cohen, R.B., Meropol, N.J. Targeting signal transduction pathways in colorectal cancer – more than skin deep. *J. Clin. Oncol.* 23(23):5374-5385, 2005.

Cohen, R.B., Gallant, G., Tolcher, A.W. Regulatory barriers to phase I clinical studies in the United States: Can we find common ground among clinical investigators, industry, and the Food and Drug Administration? *ASCO Education Book*, pp. 194-98, 2005.

Kramer, N.M., Horwitz, E.M., Cheng, J., Ridge, J.A., Feigenberg, S.J., Cohen, R.B., Nicolaou, N., Sherman, E.J., Babb, J.S., Damsker, J.A., Langer, C.J. Toxicity and outcome analysis of patients with recurrent head and neck cancer treated with hyperfractionated split-course reirradiation and concurrent cisplatin and paclitaxel chemotherapy from two prospective phase I and II studies. *Head Neck* 27(5):406-414, 2005.