Leaders' Update

A message from Steven Grant, M.D., associate director for translational research

Massey continues to translate promising scientific discoveries into clinical trials.

Two recent examples of completed Massey investigator-initiated clinical trials include studies for hematologic malignancies led by Beata Holkova, M.D., and based on pre-clinical research from our laboratory. One of the trials was a phase 1 study to determine the maximum tolerated doses of a combination of the cell cycle inhibitor alvocidib and the proteasome inhibitor bortezomib in patients with B-cell malignancies such as multiple myeloma and indolent lymphoma. The rationale for this study was based on evidence of synergistic interactions between proteasome and cell cycle inhibitors in malignant blood cancer cells, a discovery made by Yun Dai, M.D., Ph.D., a member of my laboratory. The results of the clinical study, recently published in *Clinical Cancer Research*, showed three complete remissions and 10 partial remissions of the 44 patients enrolled, for a total response rate of 33 percent. The combination of the drugs was determined to be tolerable, and the regimen appears to be efficacious in patients with relapsed/refractory multiple myeloma or indolent non-Hodgkin lymphoma. We are now working with the National Cancer Institute and the involved pharmaceutical companies to develop a phase 2 clinical trial to test the effectiveness of this drug therapy.

Another recently completed trial led by Holkova was a phase 1 study involving a combination of bortezomib and the histone deacelytase inhibitor (HDACI) vorinostat for the treatment of diffuse large B-cell lymphoma and mantle cell lymphoma. The purpose of the study was to determine the maximum tolerated dose of these two targeted agents. This trial was based on laboratory evidence of synergism between proteasome inhibitors and HDACIs in various malignant blood cancers. The results, which have not yet been published, revealed multiple responses in patients with various forms of non-Hodkgin lymphoma, including some who had failed other forms of therapy.

There are also several exciting early-phase solid tumor trials that are in the process of development at Massey. A phase 1 trial poised to open in early 2015 and to be led by Andrew Poklepovic, M.D., involves neoadjuvant chemotherapy with the antimetabolite gemcitabine and the albumin-bound mitotic inhibitor nab-paclitaxel, followed by concurrent chemoradiation with gemcitabine, protein kinase inhibitor sorafenib, and vorinostat for the treatment of pancreatic cancer. The purpose of the study is to determine the appropriate doses and schedule of sorafenib and vorinostat when given with chemoradiation. The trial is based on scientific findings published in *Cancer Research* from the laboratory of Paul Dent, Ph.D. He and his research team found that vorinostat and sorafenib increase CD95 activation in gastrointestinal tumor cells through a Ca(2+)-de novo ceramide-PP2A-reactive oxygen species-dependent signaling pathway.

Another Massey trial currently in development and expected to open in the spring is a phase 1 dose-escalation trial for glioblastoma multiforme (GBM). To be led by Danielle Shafer, D.O., this trial proposes the addition of dimethyl fumarate (DMF) to standard therapy involving alkylating agent temozolomide and radiotherapy for patients with newly diagnosed GBM. DMF was recently approved for relapsing-remitting multiple sclerosis and is known to be toxic to activated microglial cells. The trial is based upon the pre-clinical work of Dent and his team, who demonstrated that microglial cells exposed to DMF result in cell death. In vivo, DMF is rapidly metabolized to monomethyl fumarate (MMF), which appears to be synergistic with both radiation and temozolomide in multiple human GBM cell lines. Furthermore, MMF does not interfere with the cytotoxic effects of temozolomide in numerous human GBM cell lines.

Finally, Massey has recently added several physician-scientists and continues to recruit for various positions that would increase our translational research capabilities. New faculty members participating in our early phase program include Victor Yazbeck, M.D., who is involved in lymphoma research; Sosipatros Boikos, M.D., whose work centers on sarcoma and other solid tumors; and Giao Phan, M.D.,

who focuses on immune checkpoints.

Please visit the **Massey news blog** for more information about the cancer center's translational research.

Regards,

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