Paul Chapman

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Paul Chapman, MD, senior author of the study and an attending physician on the Melanoma and Sarcoma Service at Memorial Sloan Kettering

“Metastatic melanoma is a very challenging disease to treat and there have been no significant therapeutic advances in the past 20 years. What has changed is that we learned that half of melanomas are addicted to a mutated gene called *BRAF*; this new targeted drug inhibits *BRAF* and shuts off these tumors. We have seen many tumors shrink rapidly and, in some patients, quality of life improved dramatically,” said Paul Chapman, MD, senior author of the study and an attending physician on the Melanoma and Sarcoma Service at Memorial Sloan Kettering. “This is the beginning of personalized medicine in melanoma.”

Genetic mutations in the *BRAF* gene occur in 40 to 60 percent of patients with melanoma and offered the investigators an opportunity to test targeted therapy in this disease. PLX 4032, which targets and blocks the BRAF protein at the cellular level, is

an oral medication taken twice daily.

The multicenter, phase I dose-escalation trial was followed by an extension of the trial at the phase II recommended dose. Fifty-five patients were enrolled in the dose-escalation portion of the study. Screening for *BRAF* mutations was not a requirement for study entry during this phase, but as the trial progressed, an increasing percentage of patients were prospectively identified as having this mutation. Later, 32 additional patients, all with *BRAF*-positive melanomas, were treated at the maximum tolerated dose in the extension phase.

In the phase I dose-escalation group, ten partial responses and one complete response were noted among 15 melanoma patients with *BRAF* mutations who were treated with moderate to full doses of drug. Tumor shrinkage was seen at all sites of metastatic disease including the liver, small bowel, and bone. The duration of responses ranged from 3.3 months to more than 19 months with four responses still ongoing.

In the extension group, two complete and 24 partial responses were seen among the 32 patients treated with a full dose of drug. To date, 16 of 32 patients are still on the study, and the estimated median progression-free survival among these patients is at least seven months.

The side effects of PLX4032 were relatively minor and included rash, nausea, photosensitivity, fatigue, and low-grade skin tumors called squamous cell carcinoma, keratoacanthoma type. These are removed easily and in no case did they cause patients to come off treatment.

A phase III trial of PLX4032 is currently underway. Principal Investigator of the phase III trial Dr. Chapman says, “We have never seen an 80 percent response rate in melanoma, or in any other solid tumor for that matter, so this is remarkable. The tumor responses induced by PLX4032 are not always long-lasting though, and we don’t know if treatment really improves overall survival of melanoma patients. That is what we are trying to find out in the ongoing phase III trial. In the future, we hope to combine PLX4032 with other anti-melanoma drugs currently being developed.”

According to the National Cancer Institute, more than 68,000 new cases of melanoma were diagnosed in the United States in 2009, and more than 8,600 Americans died from the disease.

Colleagues and co-investigators on this work are affiliated with Abramson Cancer Center of the University of Pennsylvania, Massachusetts General Hospital Cancer Center, Vanderbilt University, The University of Texas M.D. Anderson Cancer Center, the University of California, Los Angeles, and Peter MacCallum Cancer Centre, in Melbourne, Australia. This work was supported by Plexxikon Inc. and Roche Pharmaceuticals.