Targeted drug leads to regression of metastatic melanoma with mutated BRAF gene

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Use of an experimental targeted drug to treat metastatic melanoma tumors with a specific genetic signature was successful in more than 80 percent of patients in a phase 1 clinical trial. Results of the trial of PLX4032, an inhibitor of a protein called BRAF that is overactive in more than half of all melanomas, appear in the August 26 *New England Journal of Medicine*.

"Metastatic melanoma has a devastating prognosis and is one of the top causes of cancer death in young patients," says Keith Flaherty, MD, director of Developmental Therapeutics at the Massachusetts General Hospital (MGH) Cancer Center, lead and corresponding author of the NEJM article. "Until now, available therapies were few and unreliable, so these findings can really change the outlook for patients whose tumors are fueled by this mutation."

Although surgical removal is usually successful in treating early-stage melanoma, once the skin tumor has spread to other sites in the body, the outlook has been grim. The two FDA-approved drugs - interleukin-2 and dacarbazine - produce a response in only 10 to 20 percent of patients. The current prognosis for survival in metastatic melanoma is 9 months or less, with 9,000 people dying in the U.S. each year.

The role in melanoma of the BRAF mutation - which keeps the protein constantly activated and driving cell growth - was discovered in 2002 by

researchers at the Sanger Institute in Britain. Flaherty - who was then at the University of Pennsylvania Abramson Cancer Center - began to explore whether drugs targeting the mutation might interfere with tumor growth. After one potential drug was not effective, he began working in collaboration with Paul Chapman, MD, of Memorial Sloan-Kettering Cancer Center in New York to study PLX4032, an agent developed by Plexxikon and licensed to Roche Pharmaceuticals. Initial trial results were disappointing, but a new formulation that increased the bioavailability of PLX4032 proved to have rapid results that are being reported in the NEJM paper.

The initial stage of the study - led by Flaherty, Chapman and colleagues at six sites in the U.S. and Australia - was designed to establish the effective dose. It enrolled 55 cancer patients, most with metastatic melanoma, who received escalating doses of PLX4032 until unacceptable side effects occurred. BRAF mutations were present in the melanomas of 16 participants in the latter part of this stage, and in 11 of those patients, tumors quickly shrank or, in one instance, disappeared. Three participants with BRAF-mutated thyroid cancers also had their tumors shrink or stabilize in response to PLX4032 treatment.

The second stage enrolled 32 patients with BRAF-mutated melanoma who received the PLX4032 dosage established in the first phase: 960 mg twice a day. In 26 of those participants, tumors shrank more than 30 percent, meeting the criteria for clinical response, and completely disappeared in two. Since another two participants had some reduction in the size of their tumors, Flaherty projects that PLX4032 appears to shrink tumors in approximately 90 percent of patients with BRAF-mutated melanomas.

"One of the things that make these results truly remarkable is that this drug works so reliably," he explains. "And patients who have been experiencing symptoms like pain and fatigue begin to feel better within a

week of starting treatment, giving them a much better quality of life.

As seen in trials of other targeted cancer treatments, resistance to PLX4032 developed in the tumors of many participants, leading to resumed tumor growth. Currently tumor suppression has been maintained from about three months to longer than two years, with an average progression-free survival of eight months, and follow-up studies are exploring how resistance occurs and potential strategies to get around it. Two additional MGH-based clinical trials are now underway - a phase 2 study in patients unsuccessfully treated with the FDA-approved drugs, enrollment for which is complete, and a larger phase 3 study that compares PLX4032 with dacarbazine in newly diagnosed patients.

"Until now, we've never had a credible first treatment option for metastatic melanoma, so this has completely transformed how we approach treatment for patients with the BRAF mutation," says Flaherty, who is a member of the Harvard Medical School faculty. "Although we don't know how long response may last, the ability to beat this disease down in the short term will buy us time to strategize second-line therapies and design the next generation of trials."

Provided by Massachusetts General Hospital

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