The findings are potentially practice-changing for a historically "untreatable disease." Though uveal melanoma is rare — there are only 2,500 cases diagnosed in the United States each year — about half of patients will develop metastatic disease, and survival for patients with advanced disease has held steady at nine months to a year for decades.

Researchers found that progression-free survival (PFS) in patients receiving selumetinib was nearly 16 weeks and 50 percent of these patients experienced tumor shrinkage, with 15 percent achieving major shrinkage. Patients receiving temozolomide, the current standard chemotherapy, had seven weeks of PFS and no tumor shrinkage. Selumetinib also lengthened overall survival to 10.8 months versus 9.4 months with temozolomide, and side effects were manageable.

“This is the first study to show that a systemic therapy provides significant clinical benefit in a randomized fashion to advanced uveal melanoma patients, who have very limited treatment options,” said Richard D. Carvajal, MD, a medical oncologist at Memorial Sloan Kettering and lead author on the study. “This clinical benefit has never been demonstrated with other conventional or investigational agents, which is all we have been able to offer patients for decades.”

Dr. Carvajal and his team decided to test selumetinib because it blocks the MEK protein, a key component of the tumor-driving MAPK pathway. This pathway is activated by mutations in the *Gnaq* and *Gna11* genes, which occur in more than 85 percent of uveal melanoma patients; 84 percent of patients in this trial had one of the mutations.

Uveal melanoma does not respond to the drugs given to patients with melanoma on the skin; and, in fact, there is no drug approved specifically for treatment of the disease. Patients with uveal melanoma receive surgery to remove the tumor — and in some advanced cases, the entire eye — as well as radiation therapy or chemotherapy.

In the trial, researchers randomized 98 patients with metastatic uveal melanoma and administered selumetinib to 47, of which 81 percent had a *Gnaq* or *Gna11* mutation. Of the 49 patients who received temozolomide, 86 percent had a mutation. Two patients were not treated. Despite the study’s cross-over design — meaning patients whose tumors progressed on temozolomide could

begin taking selumetinib — there was a trend towards improved survival with selumetinib. Selumetinib was generally tolerable, with most side effects manageable with conservative management or dose modification.

Dr. Carvajal is currently planning a confirmatory multi-center, randomized trial that will enroll approximately 100 patients and be led by Memorial Sloan Kettering. “If we can confirm selumetinib’s effectiveness in treating advanced uveal melanoma in this follow-up trial, it will become the standard therapy for this disease, forming a foundation for new drug combinations that could maximize selumetinib’s MEK-inhibitor effect,” he said. “It could offer a whole new way to treat this historically untreatable disease.”

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