New melanoma drug Zelboraf nearly doubles survival in majority of patients

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Investigators from Vanderbilt-Ingram Cancer Center (VICC) and 12 other centers in the United States and Australia have found that a new drug for patients with metastatic melanoma nearly doubled median overall survival.

More than half of patients who were treated with the novel drug vemurafenib, known commercially as Zelboraf, responded to treatment and experienced an impressive median overall survival of nearly 16 months - far longer than the typical survival of just six to 10 months for most patients whose melanoma has spread beyond the initial tumor site.

Results from the Phase 2 trial, led by co-principal investigators Jeffrey Sosman, M.D., director of the Melanoma Program and co-leader of the Signal Transduction Program at VICC, and Antoni Ribas, M.D., professor of Hematology/Oncology at UCLA's Jonsson Comprehensive Cancer Center, were published in the Feb. 23 issue of the peer-reviewed *New England Journal of Medicine.*

"This study confirms what we have discovered in our earlier trials. Many of our patients are exhibiting a strong, immediate response to this drug and some are living significantly longer, with manageable side effects," said Sosman, professor of Medicine at Vanderbilt University Medical Center. "It was interesting to note that a few of the patients were treated with the drug for up to six months before showing convincing evidence of response."

"This study shows that Zelboraf changes the natural history of the disease," said Ribas. "These results tell us that this drug is having a very big impact, and this changes the way we treat metastatic melanoma."

Approximately half of all patients with metastatic melanoma - the most deadly form of skin cancer - have a BRAF V600 mutation in their tumor. Vemurafenib is an FDA-approved oral drug which works as a kinase inhibitor of the BRAF V600 mutation.

While vemurafenib induced clinical responses in a significant number of BRAF-positive patients when it was approved last year, the initial clinical trials had not followed patients long enough to determine overall survival.

A total of 132 patients with stage IV, BRAF-positive melanoma were enrolled in the Phase II trial. All of the patients had received at least one form of systemic treatment before enrollment in the trial.

Forty-seven percent of patients had a partial response to the drug and six percent exhibited a complete response, for an overall response rate of 53 percent.

Debra Johnson's melanoma had already spread to one of her lungs and her lymphatic system when she was referred to VICC for mutation testing. Her tumor was BRAF-positive and after more than a year on the drug, the wife and mother from New Site, Miss., says her scans are clear and there is no visible evidence of disease.

"This treatment has been an answer to my prayer," said Johnson.

The majority of patients had at least one adverse event related to the drug, but most of these were minor. The most common side effects were joint pain, rash, sun sensitivity, fatigue and hair loss. More than a quarter

of the patients (26 percent) also developed cutaneous squamous-cell carcinomas - a less serious form of skin cancer - which were surgically removed.

A Phase III trial of this same drug confirmed significant improvement in both progression-free survival and overall survival with vemurafenib over chemotherapy in an interim analysis. The Phase II study is the first to confirm the durability of the response.

While the clinical trials for vemurafenib have been positive to date, the great majority of patients eventually experience disease progression.

"We are trying to determine what is causing this drug resistance and are searching for new therapies that we can use, perhaps in combination with vemurafenib," said Sosman.

Provided by Vanderbilt University Medical Center