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Approved drug may be repurposed to treat tumors resulting from NF2-related schwannomatosis

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Patients with a genetic syndrome called NF2-related schwannomatosis (NF2-SWN) have tumors that develop on the covering of the brain or

grow along the nerves in the brain, spinal cord, and/or other locations in the body.

The new innovative clinical trial was led by Scott Plotkin, MD, Ph.D., from Massachusetts General Hospital (MGH), a founding member of the Mass General Brigham health care system.

The trial, which included the Children's Tumor Foundation, as well as major NF2-SWN expert centers (NYU Langone Health, Johns Hopkins University, Mayo Clinic, University of California, Los Angeles, University of Miami Health System, Dana Farber Cancer Institute), reveals a promising treatment for this rare and relentlessly progressive condition.

Findings from the phase 2 trial have been published in the *New England Journal of Medicine*.

"The tumors of NFS-SWN can cause a lot of problems, and there aren't any approved treatments for these tumors yet," said Plotkin, the executive director of the Pappas Center for Neuro-Oncology at MGH and a professor of Neurology at Harvard Medical School. "Progressive tumors can lead to deafness, weakness, immobility, and even death. We wanted to see if a drug called brigatinib could help patients."

Previous studies have shown that a compound called brigatinib has tumor-suppressing properties in cell and animal models of NF2-related diseases. Brigatinib is currently approved by the U.S. Food and Drug Administration to treat lung cancer.

To test brigatinib's potential against NF2-SWN, Plotkin and his colleagues gave the oral compound to 40 adult and adolescent patients who had NF2-SWN as well as tumors that were getting progressively worse. These progressive tumors fell into different

categories—vestibular schwannoma, non-vestibular schwannoma, meningioma, and ependymoma—based on their characteristics and locations.

The team found that 10% of growing tumors and 23% of all tumors shrunk in response to brigatinib. The tumors that were impacted the most were meningiomas located in the brain and non-vestibular schwannomas not along the hearing nerve. Some patients also experienced better hearing, and some said they had less pain.

The investigators noted that an important aspect of the study was that it was an "adaptive platform-basket" trial that provided an assessment of drug activity across multiple NF2-related tumor types. The adaptive design screened for futility during enrollment and preferentially enrolled patients with target tumors that were most likely to respond to treatment.

In stage 1, 20 patients were enrolled with a minimum of two patients per tumor basket. After patients were treated for six months, an interim analysis was performed and 20 additional patients with progressive tumors from the two most promising baskets were enrolled in stage 2.

"The platform-basket trial design allows rapid evaluation of investigational agents for genetic conditions with multiple manifestations," said Plotkin. "In this study, brigatinib seemed to help with different types of tumors in people with NF2-SWN."

The researchers plan to study other promising drugs in this way to determine whether drug combinations with brigatinib might further improve tumor responses in patients with NF2-SWN.

The identification of brigatinib as a potential treatment for NF2-related tumors is a direct result of the Synodos for NF2 research initiative, which was established by the Children's Tumor Foundation to foster

collaboration among leading researchers and institutions, breaking down traditional barriers in scientific research.

"We are thrilled to see the promising results of brigatinib in treating NF2-related schwannomatosis, showcasing the power of collaborative partnerships in the fight against rare diseases," says Annette Bakker, Ph.D., chief executive officer of the Children's Tumor Foundation.

"This breakthrough highlights the importance of bringing together public institutions, including NCATS, private enterprises, and nonprofit organizations to develop effective treatments that can significantly improve the lives of those affected by NF2-SWN."

More information: Scott R. Plotkin et al, Brigatinib in NF2 -Related Schwannomatosis with Progressive Tumors, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMoa2400985

Provided by Massachusetts General Hospital

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