Rare brain tumor responds to targeted tumor treatment with 'unprecedented' success

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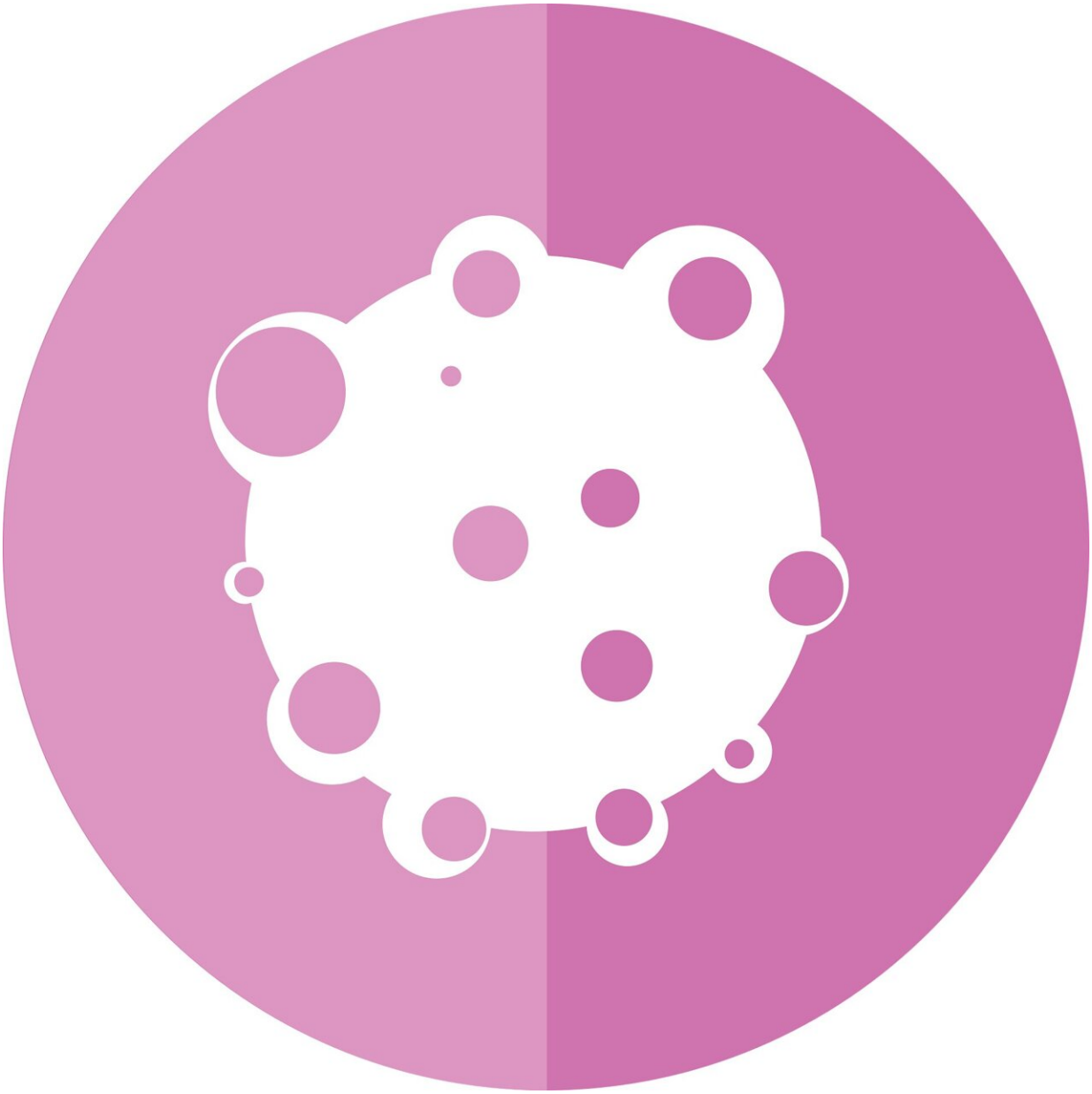

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Papillary craniopharyngiomas (PCPs) are a rare type of brain tumor that cause substantial morbidity for patients. While surgery and radiation are often used to treat PCPs, incomplete removal of the tumor and toxicity from radiation can leave patients with life-long health challenges after treatment, including neuroendocrine dysfunction or vision or memory loss.

Investigators from the Mass General Cancer Center, a member of the Mass General Brigham healthcare system, led the first multicenter treatment protocol in this rare tumor. The study was based on laboratory discoveries by Mass General Brigham researchers who studied the genetic drivers of PCP growth, uncovering that existing cancer medications can directly interfere with faulty genes in PCPs to halt their progression and drastically reduce their size. Based on this breakthrough, investigators treated 16 patients with a BRAF/MEK inhibitor as part of a phase II clinical trial and found that tumors shrank by an average of 91 percent. Results are published in the *New England Journal of Medicine*.

"All patients who completed one or more cycles of therapy responded to treatment, which is the highest response rate to date of any medical therapy for brain tumors," said first author Priscilla Brastianos, MD, director of the Central Nervous System Metastasis Center within the Mass General Cancer Center. "These unprecedented results signal a paradigm shift for targeting brain tumors because they show that, with the right target and the right drugs, precision medicine can have a dramatic impact on brain tumors."

Prior to this study, the laboratories of Brastianos and Sandro Santagata, MD, Ph.D., of Brigham and Women's Hospital's Department of

Pathology, demonstrated that approximately 95 percent of PCPs have a type of mutation in the BRAF gene, known as the BRAF *V600E* mutation, which drives their cancerous activity. This type of mutation is also present in some forms of melanoma. Recently, therapies that inhibit BRAF and a related gene, MEK, have been approved by the U.S. Food and Drug Administration for treating melanoma and some other cancers, leading the researchers to hypothesize that a BRAF/MEK inhibitor (vemurafenib/cobimetinib) might also be effective for treating PCPs.

In this multicenter, phase II trial, conducted by the National Cancer Institute-funded Alliance for Clinical Trials in Oncology Network, the researchers first screened PCP patients across the country for BRAF *V600E* mutations to identify candidates for the study. Sixteen patients at nine centers were enrolled in the study, and 15 ultimately completed at least one, 28-day cycle of the therapy. Over the course of four cycles, the median reduction in tumor size was 91 percent, with a range of 68 to 99 percent. Seven patients received no other treatment after discontinuing vemurafenib/cobimetinib and six have not demonstrated evidence of tumor progression at a median follow-up of nearly two years. No patient's tumor progressed while on vemurafenib/cobimetinib, and none have died.

Notably, patients did experience adverse reactions to the drugs. Three patients discontinued treatment due to adverse events, with one patient discontinuing therapy after eight days due to anaphylaxis and acute kidney injury. The most common adverse events were rashes, reported by six patients. Still, many patients tolerated the drugs well, electing to continue therapy beyond the four prescribed cycles as a result of their positive response to it.

Future research may determine the optimal number of cycles of vemurafenib/cobimetinib for PCP patients. The researchers are also advancing additional precision medicine clinical trials for patients with

meningiomas and brain metastases. Both use precision medicine approaches similar to the one used here to screen patients for biomarkers that indicate that their cancers may be treatable with existing therapies.

"This study demonstrated that national, biomarker-driven trials are feasible for patients with brain tumors," Brastianos said. "Moving the needle on treating rare brain tumors truly requires a multidisciplinary and multi-institution effort, and we were able to highlight that through our research."

More information: Priscilla K. Brastianos et al, BRAF–MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2213329

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