New drug could be advance against glioma brain tumors

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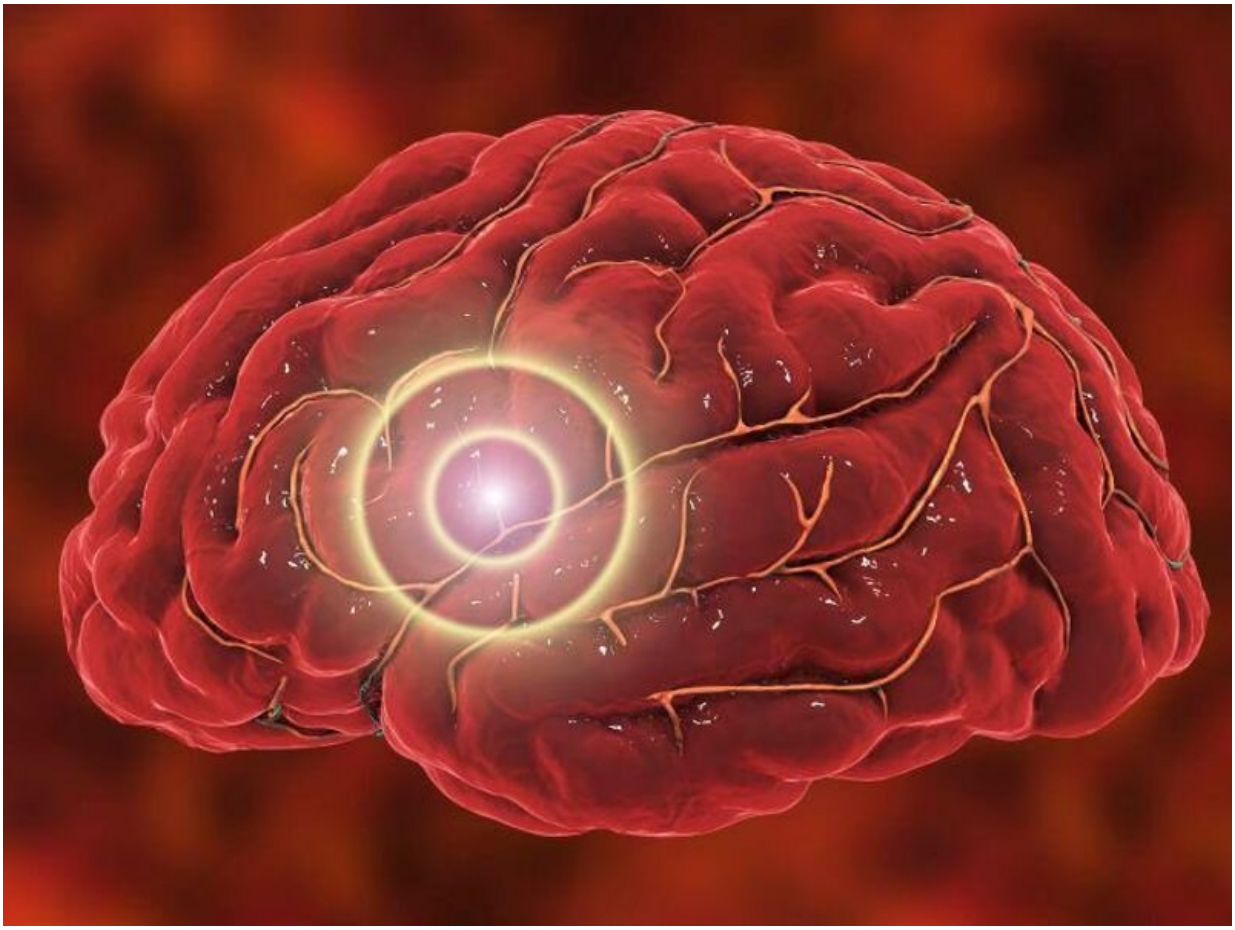

An experimental targeted therapy can dramatically slow the progress of

common slow-growing brain cancers, a new clinical trial finds.

The oral drug vorasidenib nearly tripled progression-free survival in patients with grade 2 gliomas compared to placebo, nearly 28 months versus 11 months, according to results presented Sunday at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, and published simultaneously in the *New England Journal of Medicine.*

The drug also reduced patients' risk of progression-free survival by 61% and extended the time until they require another type of treatment by 74%, said lead researcher Dr. Ingo Mellinghoff, chair of neuro-oncology at Memorial Sloan Kettering Cancer Center, in New York City.

Vorasidenib works by inhibiting mutated forms of the IDH1 and IDH2 genes, preventing them from promoting cancer growth in brain cells.

Gliomas are the most common malignant brain tumors in adults, and mutations of the IDH genes are present in nearly all grade 2 gliomas, the researchers said in background notes.

Low-grade gliomas are diagnosed in about 4,000 patients each year in the United States, said Dr. Glenn Lesser, an ASCO expert and neuro-oncologist with Atrium Health Wake Forest Baptist in Winston-Salem, N.C.

"It's a disease that affects patients who are about 40 years old, so these are young patients at the height of their professional and personal lives, with many obligations," Mellinghoff noted during an ASCO media briefing on Saturday.

The standard treatment for these gliomas is a combination of radiation and chemotherapy, which can have devastating effects on the brains of young adults, Mellinghoff and Lesser said.

As a result, many glioma patients choose a watch-and-wait approach, delaying treatment until they absolutely have to undergo it.

"There has been great concern over the long-term effects of [standard] therapy, particularly neurocognitive effects of the radiation leading to memory loss and functional decline in a proportion of the patients. If you speak to these patients, almost all of them describe some long-term effects of their therapy," Lesser said at the media briefing.

"Combine that with the fact that these tumors are typically diagnosed in people in their third, fourth and fifth decades of life, and add a prolonged survival, and it's the perfect recipe for really decimating people in the prime of their life, their most productive years, raising families," Lesser continued.

IDH mutations were first described in 2008, Mellinghoff said, and their discovery has revolutionized research into brain cancer.

Healthy IDH genes create enzymes that help break down nutrients and generate energy for cells. However, mutations in IDH genes can produce damaged enzymes that cause cells to grow out of control and become cancerous.

Gliomas driven by IDH mutations slowly infiltrate normal brain tissue and eventually become aggressive, with accelerated tumor growth fed by new blood vessels, the researchers said.

Beside gliomas, IDH mutations also have been linked to acute myeloid leukemia, bile duct cancer, bone cancer and some types of lymphoma, according to Memorial Sloan Kettering.

Other already-approved cancer drugs also target IDH, but vorasidenib was developed specifically to treat brain cancer, Mellinghoff explained,

because the drug has the ability to slip past the blood-brain barrier and treat IDH mutations inside brain tissue.

For the new trial, researchers recruited 331 glioma patients at 77 centers across 10 countries, Mellinghoff said. Half randomly received the drug, and the other half an inactive placebo.

"What's remarkable about that, this happened during the COVID pandemic," Mellinghoff said. "So, there was a real need in our patient population to come and join the study."

The results for vorasidenib in this trial were so positive that the study's safety monitoring board called an early end to follow-up so that patients who got a placebo could switch to the drug, Mellinghoff said.

"The results are quite striking," Lesser said. "They are statistically highly significant and, more importantly, they're clinically very, very significant," he stressed.

"The results of this study suggest that in selected patients with IDH mutant low-grade gliomas, we can potentially delay the use of these toxic chemotherapies and radiation for years, if not many years, and as a result, delay long-term toxicities of those therapies in a group of patients who typically are experiencing long-term survival," Lesser said.

Still, ASCO Chief Medical Officer Dr. Julie Gralow noted that vorasidenib is not yet approved by the U.S. Food and Drug Administration.

"We cannot go back and use it in clinic tomorrow, but it does have FDA breakthrough status and it's moving along fast," Gralow said. "Hopefully, we will have it available in the near future."

The study was funded by the French pharmaceutical company Servier Laboratories, the developer of vorasidenib.

More information: Ingo K. Mellinghoff et al, Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2304194

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