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Tovorafenib Approved for Some Children with Low-Grade Glioma

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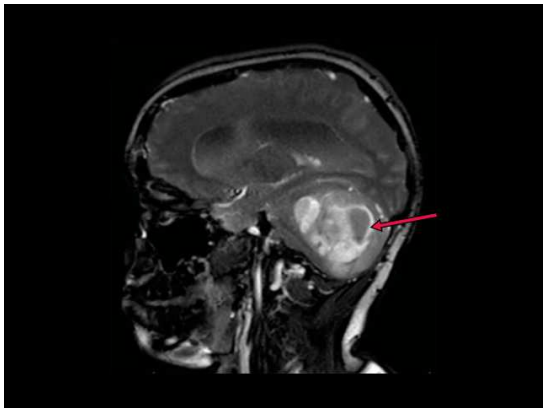
May 28, 2024, by Sharon Reynolds

On April 23, the Food and Drug Administration (FDA) granted accelerated approval to tovorafenib (Ojemda) for kids aged 6 months or older who have low-grade glioma, a type of brain tumor, with changes in a gene called *BRAF*.

The approval applies to tumors that can't be completely removed with surgery or have come back after surgery. To receive tovorafenib, children must also have already received one prior systemic treatment, such as chemotherapy, after surgery.



An MRI scan of a child with a low-grade glioma near the cerebellum.
Credit: Pediatric Hematology Oncology Journal. June 2023. https://doi.org/10.1016/j.phoj.2023.04.004. CC BY-NC-ND 4.0 DEED

A combination of two drugs that also target altered *BRAF* and related genes in tumor cells, dabrafenib (Tafinlar) and trametinib (Mekinist), received a similar approval last year. But that drug combination isn't used to treat people whose tumors have *BRAF* gene changes called rearrangements or fusions, in which pieces of the gene get switched around or stuck to pieces of other genes.

Fusions are the most common changes in *BRAF* that occur in children and teens with low-grade gliomas, said Lindsay Kilburn, M.D., from Children's National Hospital, who led the study that was the basis for the new approval. So the dabrafenib/trametinib combination can't be used in many children who need treatment, she added.

Tovorafenib can target cancer cells with specific *BRAF* fusions and other changes in the gene, including mutations. In the 77-patient study that led to the accelerated approval, called FIREFLY-1, tumors shrank or disappeared entirely in almost 70% of children treated with tovorafenib.

Many of these tumors remained smaller or had not returned for more than a year at the time the initial results from the study were published in November 2023.

Trial participants are still being followed to see how long the growth of their tumors remain suppressed, Dr. Kilburn said. "But seeing [responses last] into 1 or 2 years [so far] is really exciting," she added.

A low-grade but persistent brain tumor

At first glance, low-grade gliomas—which are the most common brain tumor in children—aren't as aggressive as some other brain tumors, said Sadhana Jackson, M.D., of NCI's Pediatric Oncology Branch, who was not involved with the study.

For example, unlike glioblastoma, which spreads rapidly and invasively into brain tissue, low-grade gliomas grow slowly and do their damage by pressing into nearby parts of the brain as they expand in size.

Depending on their location in the brain, some low-grade gliomas can be cured with surgery alone. But others, if

they're adjacent to sensitive structures in the brain, can't be totally removed, Dr. Jackson explained.

"And an issue with low-grade gliomas is that some of them like to grow back," even after what appears to be complete surgical removal, she said.

Currently, most kids whose tumors can't be removed completely or come back after surgery receive chemotherapy. In some cases, chemotherapy can stop tumor growth for a long time. But the drugs used have substantial side effects, and getting chemotherapy requires regular visits to the hospital, Dr. Jackson noted.

In contrast, tovorafenib is given orally, either as a pill or a liquid, once a week at home.

"[Low-grade glioma] is often a chronic disease throughout childhood, so kids are often on and off multiple therapies," Dr. Kilburn said. Having a treatment that can be taken at home once a week, she added, "is an exciting advance from a quality-of-life perspective."

Stopping tumor growth for months or years

Tovorafenib was first developed by a company called Sunesis Pharmaceuticals, with funding from NCI's Small Business Innovation Research program. The drug was later acquired by Day One Biopharmaceuticals, which funded the FIREFLY-1 trial.

In the trial, participants aged 6 months to 25 years received the drug in cycles of four weekly doses, for as long as they appeared to be benefiting from it. Many participants in the trial had already received multiple treatments, including other BRAF-targeted drugs.

Although the main outcome measured in the study was tumor shrinkage, a reduction in the number and severity of symptoms, even if not accompanied by a substantial change in tumor size, could also be a reason to continue treatment, explained Dr. Kilburn.

After 2 years, participants were given the option to continue tovorafenib or to take an extended break—called a drug holiday. If a tumor started to grow again, tovorafenib could be restarted.

At the time the early results from FIREFLY-1 were published last November, participants had been taking tovorafenib for a median of almost 16 months, and two-thirds were still taking the drug.

About 70% of children whose tumors had a *BRAF* fusion and 50% of those whose tumors had a *BRAF* mutation called V600 had at least some measurable reduction in the size of their tumors. Overall, of the 46 children whose tumors shrank, 12 had their tumors disappear entirely, called a complete response.

Many of these tumor responses lasted for long periods. Some had already lasted for nearly 2 years at the time the initial study data was published. Participants are still being monitored to see how long responses to treatment are maintained.

The most common side effects were changes in hair color, anemia (a drop in red blood cells), changes in blood biomarkers that can be an early sign of kidney injury, and skin problems such as a severe rash. Although most side effects were considered to be manageable, 9 participants stopped treatment early because their side effects were too severe.

The study's investigators also noted that children's normal growth trajectory slowed during treatment with tovorafenib.

Brain tumors, including low-grade gliomas, can also cause growth delays, Dr. Kilburn said. So the FIREFLY-1 participants will be followed to see if normal growth resumes at the end of tovorafenib treatment and whether the treatment has long-term effects on growth.

It's important for children and their families to understand that all systemic treatments have side effects, but the

benefit of treatment may well outweigh the impact of the problems caused by the tumor if it continues to progress., Dr. Jackson said.

However, some of these side effects can be permanent, she added, which "highlight the importance for [life long] survivorship care for these kids."

More tools in the toolbox

Based on the promising results of FIREFLY-1, a larger randomized clinical trial, called FIREFLY-2, has been launched to compare tovorafenib with chemotherapy as an initial treatment for children with low-grade gliomas that have fusions, rearrangements, or mutations in *BRAF* or several related genes.

A separate clinical trial is comparing the targeted therapy selumetinib (Koselugo) with chemotherapy as an initial treatment after surgery for children with low-grade glioma regardless of whether their tumors have *BRAF* changes. Selumetinib blocks the activity of a protein called MEK, which is part of the same growth-promoting communication network in glioma cells as mutant BRAF proteins.

"Both of these trials will be really important to [guide] whether these targeted therapies get integrated into treatment earlier on," said Dr. Kilburn.

"Until the last 10 years, we didn't have a way to directly target some of the known [genetic changes] in these tumors," Dr. Jackson said. "The approval [of tovorafenib] is great for children, and it's great to have more tools in our toolbox."

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