How research helped lead to FDA approval of a pediatric neuroblastoma drug

December 15 2023, by Ashley WennersHerron

Credit: Unsplash/CC0 Public Domain

In 2003, the first year of her fellowship in pediatric oncology, two of Giselle Saulnier Sholler's first three patients had died from neuroblastoma, closely matching the 30% survival rate expected at the

time for high-risk neuroblastoma. She knew research was the only way to change these outcomes.

Now, 20 years later, the U.S. Food and Drug Administration (FDA) has approved the first drug—based on Sholler's research and clinical trials she led through the Beat Childhood Cancer Research Consortium—to reduce the risk of relapse for pediatric high-risk neuroblastoma patients.

"Neuroblastoma is rare, with only 800 cases diagnosed in the United States each year," said Sholler, who is now the division chief of pediatric hematology and oncology at Penn State Health Children's Hospital and the director of pediatric oncology research at Penn State College of Medicine.

"I am so thankful that our research studying this drug, both in our laboratory and through clinical trials, over the past 14 years has brought so much hope to our pediatric oncology teams and the families of children with high-risk neuroblastoma."

Neuroblastoma is a cancer that develops primarily in children less than six years old. It originates in immature nerve cells found in several areas of the body, most commonly in the adrenal gland and next to the spine. About 50% of the patients already have advanced metastatic disease by the time they are diagnosed, with spread to lymph nodes, bones, bone marrow and liver most commonly. Of these high-risk patients, Sholler emphasized that about 40% of those who enter remission will relapse within four years, and of those, fewer than 10% will survive five more years.

The drug, called eflornithine (DFMO) and newly branded as IWILFIN by US WorldMeds, reduces the risk of relapse for pediatric high-risk neuroblastoma patients achieving at least a partial response after multiagent, multimodality therapy including immunotherapy by more

than 50%.

This finding was the result of a trial analysis led by Sholler and the Beat Childhood Cancer Research Consortium in collaboration with US WorldMeds. The study has been published in the *Journal of Clinical Oncology* . According to Sholler, the evidence provided by this study led directly to FDA approval.

"Dr. Sholler and her team have an unwavering singular focus on doing what is best for the children in the clinic today," said Patrick Lacey, who founded the Beat Childhood Cancer Foundation and has a child with neuroblastoma.

"That belief drives everything they do and mirrors the indefensible hope that we have as parents of children with cancer that something can be done. This drug approval has the potential to dramatically change the landscape for kids with neuroblastoma, and it all started with the belief that it was possible—followed by the sheer determination to take every step necessary to achieve that goal. We are fortunate to be able to help to fund these efforts to help improve survival for children who need our help."

Kristen Gullo, vice president of development and regulatory affairs at US WorldMeds, spearheaded the company's efforts.

"We are thankful for our collaboration with the Beat Childhood Cancer teams to be able to make such a difference in the lives of children with cancer," said Gullo, whose family was also touched by neuroblastoma.

Yatin M. Vyas, professor and chair of the Department of Pediatrics in the Penn State College of Medicine and pediatrician-in-chief of the Penn State Health Children's Hospital, echoed the sentiment.

"Collaborations among clinicians, researchers, industry and the people most directly affected by pediatric cancer—our patients' families—can produce incredible results," said Vyas, who is also the vice president of Penn State Health Children's services and the Children's Miracle Network and Four Diamonds Endowed Chair.

"It is this type of dedicated work that can change lives, and we are proud of Dr. Sholler and grateful for her commitment to improve outcomes for what has been such a devastating disease."

How it all began: Funding hope

Neuroblastoma tumors have highly activated expression of the ODC1 gene, which helps facilitate polyamine synthesis. Polyamines are molecules involved with cell proliferation and longevity, among other responsibilities. But too many polyamines can lead to uncontrolled cell division, or cancer.

"Preventing relapse is the goal to ensure long term survival for children," Sholler said.

Bolstered by encouraging laboratory research, the FDA approved a Phase I clinical trial to test the safety of DFMO in children with incurable neuroblastoma—which would require significant funding. Sholler turned to the parent-led advocates and foundations that supported her earlier research and trials.

"These families merged together to form the Beat Childhood Cancer Foundation to honor all of their kids, and they fund the bulk of the work we do in the Beat Childhood Cancer Research Consortium," said Sholler, who founded and chairs the international consortium that now comprises more than 55 universities and children's hospitals throughout the U.S. and Canada who are committed to discovering new therapies

and cures for pediatric cancer.

Before the foundation and consortium formed, though, Lacey spearheaded the fundraising needed for Sholler to launch the trial.

Three survived

In the first trial in 2010, 17 children who were considered to be incurable enrolled. Three of the study participants survived. Sholler said she realized that DFMO was having a dramatic effect, but only in some patients. While investigating this, she discovered that DFMO inhibits LIN28, a signaling pathway that contributes to the survival of cancer stem cells, the malignant cells that can seed tumors and cause relapses in patients. She also demonstrated that by blocking LIN28, this drug could prevent existing cancer stem cells from forming tumors.

In 2012, she launched a new trial focused on high-risk neuroblastoma children in remission, using DFMO as a maintenance therapy to prevent these children from relapsing and increase survival rates.

"In this trial, which we published in *Scientific Reports* in 2018, we saw that 97% of the kids who took DFMO twice a day for two years survived and 84% stayed in remission," Sholler said. "After four years, 96% of the kids were still alive and 83% were still in remission."

She continued the work, analyzing DFMO's ability to keep neuroblastoma relapse at bay. The issue was that her clinical trial was a single-arm study, meaning every enrolled patient received the treatment. Every drug the FDA has ever approved only received authorization after a randomized controlled trial in which half the participants receive the treatment and the other half receive a placebo.

Instead, Sholler and her team worked with the FDA on an approach to

externally control the study, meaning they analyzed the effect of DFMO with a separate group of patient data from another neuroblastoma study where children had received the same treatment. The only difference between the sample populations would be that the children in Sholler's trial received DFMO.

An unprecedented pathway to approval

Sholler received "Breakthrough Therapy" designation from the FDA for this work in 2020, which helps expedite testing and review for treatments that demonstrate potentially substantial improvements over available therapies. This designation led to a partnership between the drug production company supporting the research trial, Kids Cure Pharmaceuticals, and US WorldMeds to streamline and scale DFMO production.

The drugs went to more than 850 pediatric cancer patients in more than eight trials under the Beat Childhood Cancer Research Consortium, led by Sholler.

"With our most recent analysis, we saw that patients receiving DFMO were twice as likely to experience event-free survival—meaning no relapse—and three times as likely to survive overall as compared to historical rates of neuroblastoma patients treated with the standard of care without DFMO," Sholler said.

With the results from the analysis published in the *Journal of Clinical Oncology*, US WorldMeds applied for FDA approval to make DFMO commercially available for neuroblastoma relapse prevention. Sholler and the company presented the results to the FDA's Oncologic Drugs Advisory Committee on Oct. 4. The committee—which comprises independent national experts who review the safety and efficacy data and advise the FDA on whether they believe the data are scientifically

sound—voted 14 to 6 that DFMO shows evidence of reducing the risk of neuroblastoma relapse.

"There was an outpouring of support from the community for the committee to recommend approval," Sholler said. "More than 160 families wrote letters to the FDA advocating for DFMO before the meeting."

Ten weeks later, with the evidence provided and the committee's recommendation, the FDA approved DFMO. It will be commercially available under the name IWILFIN in early 2024. The name is a combination of two patients: Will, who was the first long-term survivor from the 2010 Phase I trial and has been in remission for more than a decade, and Finn, another survivor that inspired US WorldMeds to join the fight against high-risk neuroblastoma, completing the partnerships necessary to bring DFMO to patients.

"It's amazing—together, we have made a difference," Sholler said. "I look back 20 years, and we made the change I only imagined at the start of my fellowship. With the help of the families, our research partners, US WorldMeds and so many others, it's clear that research extends beyond testing drugs. It provides hope for every family affected by pediatric cancer."

More information: Javier Oesterheld et al, Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score–Matched Survival Outcome Comparisons, *Journal of Clinical Oncology* (2023). DOI: 10.1200/JCO.22.02875

Provided by Pennsylvania State University