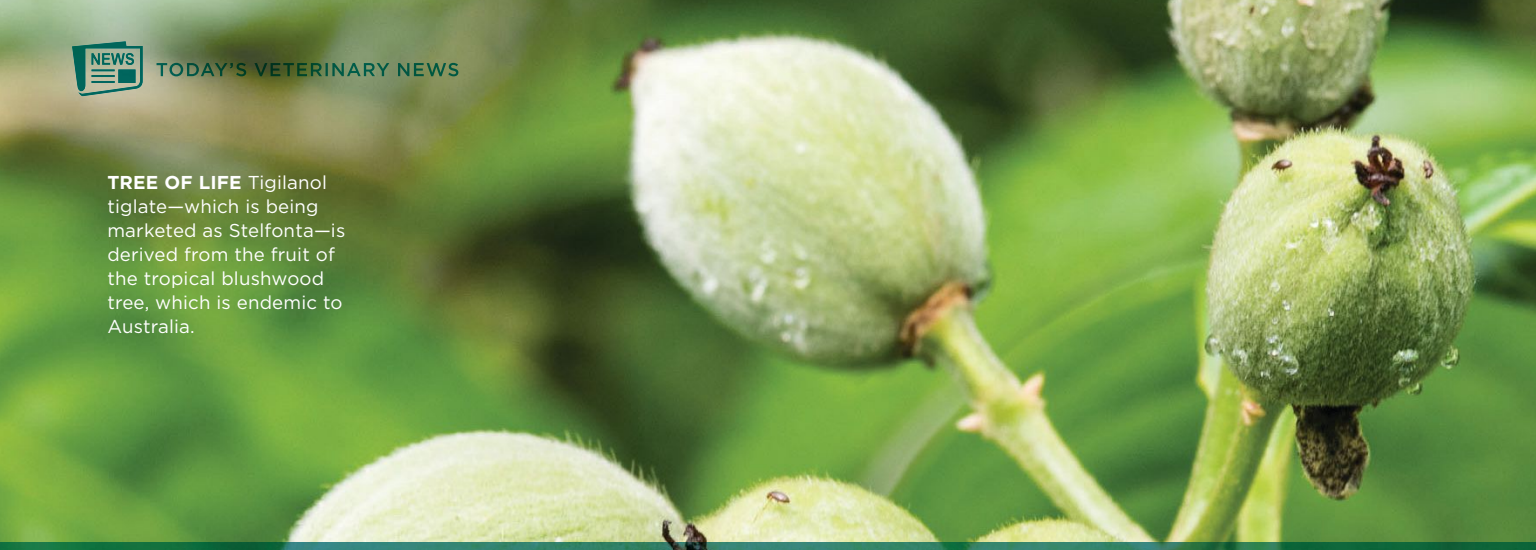

TREE OF LIFE Tigilanol tiglate—which is being marketed as Stelfonta—is derived from the fruit of the tropical blushwood tree, which is endemic to Australia.

ONCOLOGY NEWS

Targeted Therapy

***Patricia Wuest**, Vice President, NAVC Media Strategy*

In 2014, researchers published the results of a study in the journal *PLoS One* that showed the complete destruction of tumors in 75% of laboratory mice treated with direct injections of EBC-46 into the cancerous cells.[1] Conducted by a team of scientists at the Queensland Institute of Medical Research in Australia, as well as the pharmaceutical company QBiotics, the study results showed that "the response and cure was enduring, as demonstrated by the lack of relapse of MM649 tumors over a period of 12 months."[1]

Human clinical trials soon followed, and between November 2016 and March 2018, a field study of 123 dogs with mast cell tumors found similarly encouraging results as the 2014 clinical trial involving mice.[2] A single injection of tigilanol tiglate (EBC-46) removed 75% of the tumors at day 28, which was significantly higher compared to untreated controls; at day 84, 93% showed no recurrence of the tumors.[2]

"To have such a high response rate for a cancer drug is not super common," says one of the study authors, Chad Johannes, DVM, DACVIM (SAIM, Oncology), assistant professor at Iowa State University's College of Veterinary Medicine. By comparison, "many of the anti-cancer drugs we use from the human side for mast cell tumors, you might get a response in the 40% to 50% range—so we were quite happy."

Tigilanol tiglate is derived from the fruit of the tropical blushwood tree (*Fontainea picrosperma*), which is found only in the rainforest in Far North Queensland, Australia. QBiotics developed and holds the patent to tigilanol tiglate and with their marketing and distribution partner Virbac is marketing it as Stelfonta®. Stelfonta has been approved for veterinary use in Europe; it is in late-stage regulatory review by the FDA's Center for Veterinary Medicine in the U.S.

"Lymphoma is the most common cancer we see in dogs," says Dr. Johannes. "Mast cell tumors can look and act like anything—I think that's why they're so frustrating. Oftentimes, they can come up pretty quickly, and while they can be static, more often than not, they can be aggressive."

The patients in the 2016-18 study had a single, new mast cell tumor (up to 10^3 cm in size). They were either treated with Stelfonta or monitored in a control group. Four weeks after the first treatment, the tumors in 75% of the dogs that received Stelfonta (60 out of 80) had completely disappeared compared to 5% of dogs in the control group that received no treatment. The dogs that had not responded to Stelfonta after 4 weeks were treated with a second dose, and roughly half of those had a favorable response. Overall, 87% (68 out of 78) had a complete response with Stelfonta.[2]

Courtesy Scott Hartvigsen

Tigilanol tiglate stimulates the action of enzymes called protein kinase C, which are involved in regulating processes that can help cells grow.

HOW IT WORKS

Tigilanol tiglate stimulates the action of enzymes called protein kinase C, which are involved in regulating processes that can help cells grow. When protein kinase C enzymes are activated, they interrupt the blood supply to cells, resulting in the death of those cells. The drug also activates the body's immune system to promote wound healing.

"It helps stimulate epithelial cells, the cells that come in and help promote healing," says Dr. Johannes. "You get nice wound closure, and by day 28 to day 42, the tumor sites are healed."

EDUCATING VETERINARIANS AND CLIENTS

Stelfonta is not expected to replace conventional removal of mast cell tumors in dogs,[3] but rather will be an option when surgical removal is not possible or presents a challenge.

"For probably 80% of dogs with mast cell tumors, surgery is the treatment of choice," says Dr. Johannes. But dogs undergoing surgery require sedation or anesthesia, which can pose an increased risk for older dogs and brachycephalic breeds. In addition, a successful outcome depends on getting "wide and deep margins, so that we increase the likelihood of getting it all and decrease the chance that it recurs locally," he says. "Sometimes, it is difficult to do that—40% to 50% percent of mast cell tumors occur on the limbs and those are very hard to get wide and deep margins. This will be a nice option."

Client education will be critical, says Dr. Johannes. Injecting Stelfonta into the tumor causes "a fair amount of bruising and edema to occur, especially in the first 3 or 4 days," he notes. "As the tumor sloughs off, there will be an open wound that is going to be there until day 28 to 42. We've learned through clinical trial and error how this drug works and it is counterintuitive to how we usually manage wounds as far as keeping them bandaged and those types of things. It changes a veterinarian's approach to managing wounds. We keep these wounds open, and even if the dog is licking, it's probably not a bad thing."

The decision to use Stelfonta to treat mast cell tumors will have to be considered on a case-by-case basis, says Dr. Johannes. "Any time a new therapy comes out, especially a new route of delivery and a new mechanism of action, we're going to have to learn how we incorporate it into case management and which cases are the best for selection. We don't know everything yet. It's going to be a learning curve, and it will grow and evolve as we get more experience and comfort level with it."

THE FUTURE IS BRIGHT FOR VETERINARY ONCOLOGY

Dr. Johannes, who is an advisory board member and member of a consulting panel of veterinarians for QBiotics, also helped launch Pfizer Animal Health's Palladia®, the first FDA-approved canine cancer drug, in 2009. "In the last 11 years, it's been fun to watch the growth of the oncology market," he says. "There are a lot of companies, both large and small, that are engaged with bringing us new therapeutics. For decades, we've relied on human generics as our treatment. As human oncology evolves, the challenge is that we're less able to take those human drugs as generics and put them into dogs because they're speciated drugs. They may not be effective and may be detrimental. Having drugs developed for our [animal patients] with a known safety profile is critical. We really haven't moved the needle much in the last 10 to 20 years for many canine cancers. To have new therapies that can move the needle is going to change how veterinarians manage cancer in their patients." TVP

References

1. Boyle GM, D'Souza MMA, Pierce CJ, et al. Intra-lesional injection of the novel PKC activator EBC-46 rapidly ablates tumors in mouse models. *PLoS One* 9(10):e108887.
2. De Ridder TR, Campbell JE, Burke-Schwarz C, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). onlinelibrary.wiley.com/doi/full/10.1111/jvim.15806. Accessed July 11, 2020.
3. Garrett LD. Canine mast cell tumors: diagnosis, treatment, and prognosis. *Vet Med (Auckl)* 2014;5:49-58.