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Single-patient data suggest Tiziana nose a better way with CD3 in MS

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Tiziana Life Sciences Inc. (https://www.cortellis.com/intelligence/qsearch/Tiziana%20Life%20Sciences?indexBased=true&searchCategory=ALL)'s intranasal, fully human anti-CD3 monoclonal antibody will need testing in 10 or 20 more patients to confirm the signal in secondary progressive multiple sclerosis (SPMS), but key opinion leaders on a conference call March 14 sounded optimistic as they checked out the prospect's early efficacy.

Microglial activation was inhibited in one patient at six months, as shown by a positron emission tomography (PET) scan, and pro-inflammatory cytokines were down-regulated. Based on the findings at Harvard Medical School's Brigham and Women's Hospital, the FDA has allowed a second patient to get the drug under a single-patient expanded access IND.

"We have shown and others have shown that the microglial PET signal is very tightly linked with patients' clinical disability" in SPMS, said Tarun Singhal, assistant professor of neurology at Harvard. Asked whether longer treatment with foralumab would likely show more improvement, he allowed for such a "possibility. Obviously there will be a bottom-line point where it won't be able to reduce further. That remains to be seen," he said.

The patient's disease had steadily worsened despite several MS therapies, including B-cell depletion, with gait and limb strength deteriorating over the previous two years. Foralumab stabilized the disease course and based on the success, regulators gave the go-ahead for researchers to continue treatment for another six months.

Howard Weiner, professor of neurology at Harvard, said he's been working in the field for decades. "When I started, there was no treatment" for MS, he said. Today, patients have drugs available for relapsing/remitting disease, most prominently B-cell therapies and steroids for acute attacks, but a major need remains in non-active disease that continues to advance. "We can shut down the attacks, but [patients] keep progressing," he said. "We think this is related to a compartmentalized response in the brain involving microglial cells." At his clinic, "one patient after another [asks,] 'Doctor can you give me anything?' and everything we've tried doesn't work."

Enter foralumab (https://www.cortellis.com/intelligence/qsearch/foralumab?indexBased=true&searchCategory=ALL), delivered orally or up the nose. "The beauty of it is that it's physiologic and it's safe," Weiner said, noting that CD3 reacts with T-cell receptors. In 2006, researchers published their first paper on the strategy in *Nature Medicine*. A daily nasal treatment in animal models with the anti-CD3 antibody brought "a dramatic effect on progression. Many people think that we're giv-

ing [the drug] to get into the brain, but that's not the case," he said. Instead, it localizes in lymph nodes, "works in the periphery, and then cells go into the brain. We don't really worry about the blood-brain barrier. We're not getting the antibody in the brain, we're stimulating the immune system – a very important point."

Foralumab also holds promise in Alzheimer's disease, Crohn's disease (CD) and type 1 diabetes. In early February, Tiziana, of New York, submitted an amendment to the IND application for an oral version intended to become the first take-home immunotherapy in patients with mild to moderately active CD. If accepted by the FDA, the amendment is expected to expedite patient enrollment and completion of the foralumab phase Ib study by the fourth quarter of this year, the company said.

Tiziana has a licensing arrangement with Durham, N.C.-based Precision Biosciences Inc. to explore the drug as an agent to induce tolerance of allogeneic CAR T cells to potentially improve outcomes. Wainwright analyst Patrick Trucchio, who covers Precision, said in a Nov. 17, 2021, report that foralumab "will have a strong potential in differentiating Precision's programs allowing administration routes preferable for patients."

CD3 has been in the headlines often this year. In January, Immunocore Holdings plc won (https://www.bioworld.com/articles/515478-immunocore-wins-us-fda-approval-for-pioneering-uveal-melanoma-drug) FDA approval of the uveal melanoma drug Kimmtrak (tebentafusp-tebn), the first T-cell receptor (TCR)-based therapy to reach the market, the first approval for a drug targeting gp100, and the first drug approved in 40 years for the cancer, which is the most common eye cancer in adults, though still rare. A bispecific TCR attached to an anti-CD3 immune effector function, Kimmtrak targets gp100, an antigen expressed in melanocytes and melanoma.

The news hasn't always been good. In late February, reports (https://www.bioworld.com/articles/516487-celyad-pauses-phase-ib-trial-in-colorectal-cancer-in-latest-car-t-solid-tumor-setback) of two patient deaths prompted Celyad Oncology SA, of Mont-Saint-Guibert, Belgium, to voluntarily pause a phase Ib trial testing its allogeneic CAR T-cell therapy, CYAD-101, in combination with Keytruda (pembrolizumab, Merck & Co. Inc.) in patients with refractory metastatic colorectal cancer. CYAD-101 comprises full-length human NKG2D co-expressed with a TCR inhibitory molecule peptide consisting of a truncated form of CD3 zeta. The latter component is meant to interfere with TCR signaling and avoid the graft-vs.-host risk associated with allogeneic T-cell therapy.

In SPMS, laboratory explorations continue. The journal *Neurology* this month published findings (https://n.neurology.org/content/early/2022/03/11/WNL.0000000000200144) on the relationship between slowly expanding lesions (SELs) on magnetic resonance imaging (MRI) and disability in the disease. Studied retrospectively were 345 patients with SPMS enrolled in the MS-Smart trial (https://clinicaltrials.gov/ct2/show/NCT01910259), sponsored by University College in London and set up to test three separate drugs against placebo. "Definite SELs represent almost one-third of T2 lesions in SPMS," the authors concluded. "They are associated with neurodegenerative MRI markers and related to clinical worsening, suggesting that they may contribute to disease progression and [could] be a new target for therapeutic interventions."