May 28, 2024

Dear CIRM Application Review Subcommittee members,

My name is Jonathan Blum, and I was diagnosed with ALS in 2020, about a month after I retired. For background, I have an MD and a PhD from UCSF, and I was an infectious disease specialist and hospital epidemiologist until my retirement. I have had relatively slow progression of my disease.

I was asked by EverythingALS to comment on TRAN1-16013 from AcuraStem for the development of AS-241, an ASO targeting UNC13A, specifically regarding whether intrathecal therapy would be acceptable to ALS patients. I have no financial interest in the company or its products, I'm receiving no compensation for this comment, nor do I stand to benefit clinically from any future product. In addition, I agreed to comment before AcuraStem or EverythingALS knew what my statement would be, and they had no substantive input into my statement. In other words, I was not cherry-picked for my response.

The current standard of care for ALS, in addition to supportive care, involves two medications of very limited efficacy. A third drug was just removed from the market by the manufacturer after failing in a phase 3 trial. Although much scientific progress is being made, neurodegenerative disorders are a tough target, and it is very likely that options will remain quite limited for some time. In other words, there is no miracle pill on the horizon.

Although there is no denying that intrathecal therapy is less convenient than pills, I believe it is not a substantial obstacle to use of such a therapy. There are several good reasons for this. First, intrathecal therapy is already used for other serious diseases, such as leukemia, spinal muscular atrophy, or in my field, fungal meningitis. Second, intrathecal antisense therapy is actually already being used for ALS in the small group of patients who have a mutation in the SOD-1 gene, and it is the first ALS treatment that has been shown to reverse the disease. Uptake of intrathecal tofersen among those patients has reportedly been very high. Third, intrathecal therapy is being developed for treatment of other neurodegenerative disorders, specifically Creutzfeldt-Jakob Disease, and is even being considered as preventive therapy, prior to the onset of symptoms, in people with genetic forms of that disorder. There's a nice article about this in Science magazine on March 22.

Finally, my own perspective: I have performed many lumbar punctures, and observed how patients tolerated them. I am also facing progressive disability and certain death from my disease. There is no question that I would be willing to accept intrathecal therapy either as part of a trial, or as an approved treatment. In fact, when I enrolled in the Healy ALS Platform Trial, there was a 50% chance I would be randomized to an arm that would require two diagnostic lumbar punctures, and I did not hesitate. Although I was ultimately randomized to an arm that did not require lumbar punctures, my point is that for a disease with a dismal prognosis and few treatment options, lumbar punctures and intrathecal therapy are acceptable to me and other patients.

Sincerely,

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