DRUG APPROVALS

# XOMA IMMUNOCONJUGATE GETS EARLY OK

WASHINGTON, D.C.—In a day-long meeting marked by seesaw emotions, the Biological Response Modifiers Advisory Committee renewed its liberal philosophy by recommending that the U.S. Food and Drug Administration (FDA, Bethesda, MD) err on the side of biopharmaceutical approval rather than rejection. The committee advised FDA to license Xoma's (Berkeley, CA) XomaZyme-CD5+ for treating bone-marrow transplant (BMT) patients with steroid-resistant graft-versus-host disease (GvHD). How closely the agency will follow the committee's recommendation is not known. If approved, the product would be the first immunotoxin licensed in the U.S.

The drug consists of a mouse monoclonal antibody covalently bound to the cell-killing polypeptide chain of ricin, a toxin from castor beans. The antibody is directed against the CD5 antigen on T cells. These immune-system cells, which are transplanted along with the donor's marrow, cause GvHD, a disease characterized by inflammation and destruction of the skin, gastrointestinal tract, and liver. GvHD—for which the current therapy of high-dose steroids has met with limited success—affects more than half of the 4,000 BMTs performed worldwide each year. Hazardous in itself, BMT often is undertaken with other potentially debilitating treatments against various forms of cancer.

In clinical trials, the monoclonal gave rise to a "statistically significant response" among BMT patients, reported Samuel Saks, who directs clinical research at Xoma. The company conducted two trials involving 144 patients with moderate to severe steroid-resistant GvHD. It compared these patients to 157 "historical controls," or patients who underwent BMT treatment several years back. Results showed that the monoclonal induces a higher rate of complete and partial responses to treatment. It also lessens the severity of GvHD overall, produces longer-lasting remissions of GvHD, and reduces the incidence of new sites of GvHD attack. Side effects included malaise, fatigue, myalgia, and fever. The monoclonal is "an active, well-tolerated therapy," said Saks.

However, Ezio Bonvini of FDA's Center for Biologics Evaluation and Research strongly disagreed with Saks. Bonvini particularly objected to the use of historical controls, arguing that "substantial missing data for the control population raises concerns of introducing a bias in favor of treatment." Following a complex statistical analysis and allusions to possible safety problems with the drug, Bonvini asserted, "No conclusive statement can be made as to whether the Xoma drug affects the status of the patients." In other words, it does not seem to benefit patients.

The advisory committee listened attentively to both sides. It then seemed to sidestep both sets of arguments. "We've gotten bogged down in statistical analysis, with very little emphasis put on clinical effects," observed committee member Michael Hawkins from the National Cancer Institute's (Bethesda, MD) division of cancer treatment. "Why are these data not acceptable from a quality of life standpoint?" said Hawkins. "It seems to me the drug is active."

"We need to deal with this drug candidate in the clinical context of severe disease," agreed committee chairman Jerome Groopman, chief of the division of hematology and oncology at New England Deaconess Hospital (Boston, MA). "If we look at differences the way oncologists would, there are real response rates. The raw data show real numbers."

With such arguments in mind, Groopman steered the committee towards a quick vote. The momentum seemed to shape the lopsided outcome—seven to one in favor of licensing the product. "We urge Xoma to work closely with FDA in designing further studies. It should also undertake a good-faith effort to provide better control data," said Groopman.

The outcome surprised most observers. "It shows you just don't know what's going to happen," said one observer. "Perhaps the committee wants to show FDA it's not a tame puppy dog. Anyway, there's a significant element of luck" for a company bringing a product before the committee.

Uncertainty remains as to whether FDA will overturn the committee's recommendation. It could even opt for something short of full product licensing, such as a treatment IND. This would enable Xoma to sell the monoclonal, but under tighter constraints than with a full license. Also, questions about product consistency between batches—as well as safety issues—were alluded to but not aired fully during the committee meeting. The agency could invoke such issues if it is uneasy with the committee's recommendation.

**—Jeffrey L. Fox**

HUMAN GENE THERAPY

# NIHRAC APPROVES MORE CLINICAL TESTS

WASHINGTON, D.C.—Last year the National Institutes of Health (NIH, Bethesda, MD) Recombinant DNA Advisory Committee (NIHRAC) helped usher in a new era in clinical medicine by approving tests of two gene-therapy procedures in cancer patients and patients with severe combined immunodeficiency syndrome (SCID). In late May, NIHRAC approved several more gene-therapy protocols, the first of what committee members called "an avalanche" of such proposals.

The committee, however, emphatically rejected a recommendation to streamline its review of gene-therapy proposals. The sharp rise in the number of proposals led NIH's W. French Anderson—whose proposal to use gene therapy to treat SCID was the first to gain the committee's approval last year—to suggest that the Human Gene Therapy Subcommittee of NIHRAC be "dissolved," because bringing protocols before the subcommittee entails "almost a duplication of review," said French. "The point is to have more efficiency."

The response to Anderson's proposal was so dramatic that he withdrew it before the committee could formally vote to reject it. "Nobody thinks it's a good idea," said one committee member. "The two-step review expedites matters and has won the confidence of the public and of political leaders," said LeRoy Walters, an ethicist from Georgetown University (Washington, DC), who chairs the subcommittee and is a consultant to NIHRAC. Despite predictions to the contrary, the two-step process has also established an "amazing record of little controversy," said Walters.