BIOWORLD

IN THE CLINIC

Xenikos' conjugated antibody cocktail makes inroads against GvHD

By Cormac Sheridan
Staff Writer

Friday, May 27, 2016

DUBLIN – Xenikos BV is on track to complete recruitment in a phase I/II trial of T-Guard, a combination of two antibody-drug conjugates in development for treating steroid refractory graft-vs.-host disease (GvHD), in the coming months. The company expects to report survival data early next year, but, based on what it has seen so far, it is already contemplating a potentially pivotal phase II trial as its next step, which could lead to an application for conditional marketing authorization.

Xenikos, based in Nijmegen, the Netherlands, expects to report top-line data from the 20-patient trial shortly after the summer, CEO Ypke van Oosterhout told *BioWorld Today*. The primary endpoint of the open-label study is based on patients' response to therapy at 28 days, as measured by the Glucksberg grading system, which assesses the effects of GvHD on skin, the liver and the gastrointestinal tract. Intestinal involvement is a feature of the most severe cases. "That is one of the most difficult forms to treat. The survival rate is really not so high," he said. Grade III cases have a 25 percent long-term survival rate; for grade IV cases it is only 5 percent.

Six-month survival is a secondary endpoint on the trial – those data will appear in the first quarter of next year.

GvHD is a potentially fatal complication of allogeneic stem cell transplant, which arises when T cells present in the transplant recognize recipient tissues as foreign. Its incidence varies widely – according to one recent review, in the August 2015 issue of the *International Journal of Hematologic Oncology*, between 40 percent and 70 percent of patients are at risk.

T-Guard comprises two murine monoclonal antibodies, which target the T-cell receptors CD3 and CD7, respectively. Each is linked to the A-chain of ricin, the highly toxic lectin produced in the seeds of the castor bean plant (*Ricinus communis*). The twin mode of action hits T cells at different stages of maturation, but the therapy avoids the cytokine release syndrome that can accompany CD3-targeting antibodies, because the murine antibodies do not have a strong affinity for the human Fc receptor.

“It provides immediate T-cell elimination through modulation of the T-cell receptor complex,” van Oosterhout said. Hitting the CD7 antigen has twin effects. “It’s an antigen that’s expressed not only on T cells but also on natural killer [NK] cells,” he said. Although NK cells may have a protective role against GvHD, they perpetuate the problem once it becomes established. “At that stage we think it’s better to take them out,” he said.

On the basis of the first 17 patients treated so far, the trial is running at a response rate of about 70 percent. “The study is small in size so even one patient makes a big difference,” van Oosterhout said.

But the therapy appears to be at least twice as effective as the standard therapy in use at the two study centers, the Radboud University Medical Center in Nijmegen and University Hospital Münster, in Münster, Germany. That claim is based on a comparison of interim report for the first 13 patients with data from what Xenikos described as “an independently-conducted retrospective study on the institutional standard of care in the period immediately preceding this trial.”

T-Guard’s safety profile appears to be favorable as well, although given the severity of the condition it can be hard to tell. “It’s very difficult to dissect out GvHD from the toxic effects of the drug,” principal investigator Matthias Stelljes, of University Hospital Münster, told *BioWorld Today*.

That’s why a randomized controlled trial will be necessary to establish any claims of efficacy. The control treatment is likely to be physicians’ choice, given the wide variety of approaches taken to tackle GvHD once it becomes refractory to steroid therapy. Those range from calcineurin inhibitors to antibodies administered off-label, including TNF-alpha inhibitors, CD52-targeting antibody Lemtrada (alemtuzumab, Sanofi SA) and anti-CD20 antibody Rituxan (rituximab, Biogen Inc. and Roche AG), to several classes of small molecules, including mTor inhibitors and tyrosine kinase inhibitors as well as mesenchymal stem cell therapies.

Kamada Ltd., of Ness Ziona, Israel, launched this week an expanded access program to its alpha-1 antitrypsin (AAT) therapy, which it is offering to patients through the Mytomorrows web platform. “We have no well-designed prospective study to tell us what is a good drug,” Stelljes said.

“Each and every transplant center almost has its own standard of care,” van Oosterhout added.

PRIME TIME

T-Guard was one of 18 applications the EMA received for its recently launched Prime priority medicines scheme. Those selected will gain a specially designated rapporteur to guide them through the clinical development process, with the aim of helping companies avoid the methodological and clinical trial pitfalls that bedevil drug development. An announcement from the EMA on the first Prime-designated projects is imminent – it was due to finalize its selection of the first batch of projects Thursday. (See *BioWorld Today*, April 8, 2016.)

T-Guard has a clinical history stretching back about 15 years – van Oosterhout developed the therapy while working in the hematology department at Radboud University Nijmegen Medical Center. Although the original patents protecting the therapy will expire in 2024, the company also filed an additional application in 2014, based on the therapy's selective effect on depleting recently activated T cells.

Xenikos also expects to rely on data exclusivity and orphan drug provisions should the therapy reach the market. It is open to a partnering deal to further T-Guard's potential in both GvHD and other indications, such as solid organ transplant rejection and autoimmune disease.