

‘A very atypical opportunity’

Elsalys looks to cross goal line in SR-aGVHD on positive long-term OS

By Marie Powers, News Editor

Elsalys Biotech SAS, a 2013 spinout from Transgene SA, achieved a significant milestone with the finding that lead candidate inolimomab (Leukotac) showed clinical benefit during long-term follow-up of up to 8.5 years in individuals treated in the phase III study in acute steroid-resistant graft-vs.-host disease (SR-aGVHD). The positive overall survival (OS) outcome in the long-term analysis positions the Lyon, France-based company for a regulatory filing in the EU next year and puts discussions with commercial partners on the front burner – admirable achievements for a company of just 16 employees that’s raised less than €20 million (US\$22.8 million).

For patients still alive at the end of the study (23 [47 percent] and 20 [40 percent] in the inolimomab and antithymocyte globulin, or ATG, arms, respectively), OS data through May 2018 showed that inolimomab reduced the relative risk of death by 43 percent and produced a positive outcome on the composite primary endpoint at the level of statistical significance.

David Liens, the company’s chief medical officer, explained the calculation by noting that the OS endpoint was reached by 30.6 percent (15/49) and 19.6 percent (10/51) of those in the inolimomab and ATG arms, respectively, with an adjusted HR (95 percent CI) of 0.572 (0.346, 0.947), two-sided $p=0.030$. The finding represented an absolute difference in survival of 11 percent in favor of inolimomab, he said, equivalent to relative reduction of 43 percent in risk of death.

The sustained long-term efficacy of inolimomab, which has orphan drug designation in the EU and U.S. in SR-aGVHD, combined with the agent’s favorable safety profile, could bode well with regulators in an indication with a scarcity of options, suggested Elsalys CEO Christine Guillen.

Because it links specifically to a chain of the CD25 receptor, inolimomab prevents IL-2 from binding on the surface of the donor’s overactive T cells, in turn blocking their multiplication, she added. Thus, the efficacy of inolimomab in SR-aGVHD is differentiated by its specificity and preferential affinity to the CD25 receptor found on the surface of T lymphocytes.

“We are able to target only this type of cells and not the normal T cells,” Guillen told *BioWorld*. “And also with this type of format, we do not deplete the T regs, and that’s very important in this pathology because the T regs are responsible for the recovery of the patient. This is a clear mechanism of action for Leukotac and relative to the results obtained for overall

“*Leukotac is a very interesting product with a huge clinical experience and a clear mechanism of action in an indication with considerable unmet need.*”

Christine Guillen
CEO, Elsalys Biotech

survival,” which showed a clear duration of response, she added.

GVHD remains the primary complication of hematopoietic stem cell transplantation, affecting 30 percent to 55 percent of patients. Although physicians seek to combine corticosteroids with other immunosuppressive agents to treat the disease, up to half of those with aGVHD gradually become resistant to first-line treatments, and no standard of care exists for those patients.

Company weighing single and regional alliances

Established with an initial financing round of €2.1 million and a mission to develop monoclonal antibodies (MAbs) against targets in cancer and inflammatory diseases, Elsalys was co-founded by a quartet of Transgene alums, among them Guillen, former head of external collaborations at Transgene and director of project management at Opi Pharmaceuticals SA, and Thierry Menguy, head of Transgene’s Expression System Group, who heads the MAb Development and Production Unit at Elsalys.

Elsalys got off the ground with several discovery-stage oncology assets and had plans to move a lead compound into IND-enabling studies. Then, in 2015, the company acquired a dual anti-angiogenic and immunomodulating MAb from the French biotech Mablife SAS and initiated preclinical evaluation of humanized versions of the antibody in age-related macular degeneration and other retinal vascular pathologies. ELB-011, a tumor vasculature-damaging, apoptosis-inducing, cytokine cascade-promoting CD160-targeting human chimeric MAb, is independent of the VEGF pathway and designed to modulate natural killer and T cells. Elsalys is seeking a partner to advance the ophthalmology candidate, Guillen said, “since we specialize in oncology and immuno-oncology.”

A year later, Elsalys acquired from Transgene the development and marketing rights to a humanized MAb, dubbed ELB-041, targeting the colony stimulating factor 1 receptor (CSF1-R, CD115) and designed to inhibit type-2 macrophages, a highly immunosuppressive macrophage subpopulation. That program has moved into a proof-of-concept study in two fibrosis models.

In 2017, Elsalys kicked its pipeline into high gear by in-licensing inolimomab, a murine anti-interleukin (IL)-2 alpha chain (CD25) MAb, from Jazz Pharmaceuticals plc. The Dublin-based firm had gained the asset in its 2012 acquisition of privately held EUSA Pharma Ltd., which previously picked up the MAb from Opi Pharma. Although inolimomab was already in a phase II/III trial for SR-aGVHD following stem cell transplantation at the time of the EUSA transaction, Jazz was more focused on rights to Erwinaze (crisantaspase), which had shown early commercial success for the treatment of pediatric acute lymphoblastic leukemia following FDA approval in November 2011. (See *BioWorld Today*, Nov. 21, 2011, and April 30, 2012.)

With the goal of moving inolimomab to market quickly, Elsalys initially sat down in 2017 with the EMA to discuss next steps, since GVHD trials conducted by EUSA and Opi had enrolled participants in Europe, including a randomized, parallel-group phase III study examining inolimomab against usual care – ATG, approved in the indication in France – that enrolled 100 participants across 15 centers in Belgium and France. In February 2017, investigators had reported in *Blood* that the primary criteria – OS at one year without changing baseline therapy – was achieved by 14 and 11 individuals, respectively, in the inolimomab and ATG arms (hazard ratio of 0.874; $p=0.28$), falling short of the primary endpoint on a statistical basis.

But in October 2017, Jazz reported that additional analyses of the pivotal phase III study – conducted in individuals with severe with SR-aGVHD (77 percent were at grade 3 or 4) – suggested inolimomab showed promise in terms of efficacy

(37 percent reduction in the risk of death, $p=0.055$ 1-sided, and reduction of primary composite endpoint of death at one year without change in treatment 28 percent, $p=0.095$ 1-sided) and tolerability.

Last year, Elsalys presented an additional analysis of phase III safety data at the EBMT Congress in Lisbon, Portugal. Inolimomab showed a more favorable safety profile vs. ATG, with three times fewer related adverse events (14 percent vs. 41 percent, $p=0.004$) and a decrease in potentially life-threatening infectious episodes such as sepsis and septic shock (14 percent vs. 24 percent and 4 percent vs. 16 percent, respectively).

The long-term phase III follow-up data, published in *Blood Advances*, represent the first for a randomized study in SR-aGVHD, according to Guillen.

“The next step is now to meet with the EMA” to present the long-term data, she said, noting that more than 1,400 individuals have been treated with inolimomab over a 10-year period through clinical trial or compassionate use protocols. The company expects to submit its dossier next year following CMC scale-up to commercial batch quantity.

Elsalys also plans to meet expeditiously with the FDA to gain its input on the inolimomab development program and additional steps deemed necessary to register the therapy in the U.S.

Once the regulatory strategy is confirmed, the next step is to “sign an agreement for Leukotac,” Guillen said, which could involve a single partner or regional alliances, especially in China, where the candidate has attracted considerable interest, she maintained. Elsalys then plans to ink a partnership for its ophthalmology candidate, raise additional funds and begin moving other pipeline assets into the clinic.

“Leukotac is a very interesting product with a huge clinical experience and a clear mechanism of action in an indication with considerable unmet need,” Guillen said. “We have a very atypical opportunity.” ♦