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GETTING THE UPSIDE DOWN

Eleven comes back, takes Viventia via stock merger; all eyes on TPTs in cancer

By Randy Osborne, Staff Writer

CEO Stephen Hurly told *BioWorld Today* that Viventia Bio Inc.'s bid to lift antibody-drug conjugates (ADCs) "to the next level" in oncology powered a merger deal with Eleven Biotherapeutics Inc., a peer in protein engineering that's had some stumbles developing ophthalmology therapies.

Toronto-based Viventia brings cancer therapies based on antibody fragments that are genetically fused to cytotoxic proteins, which the company calls TPTs, or targeted protein therapeutics. Eleven bought all of the outstanding capital stock of Viventia in exchange for about 4 million new shares of Eleven, of Cambridge, Mass., which represented about 19.9 percent of the voting power of Eleven just before they were issued. Selling shareholders were promised post-closing contingent cash payments based on meeting milestones and on net sales related to Viventia's lead candidate, Vicinium, in a phase III trial for non-muscle invasive bladder cancer (NMIBC). Top-line results are expected in the first half of 2018.

Vicinium targets and binds to cancer cells expressing epithelial cell adhesion molecule, or EpCAM, a protein overexpressed on many epithelial cancers. The combined immuno-oncology (IO) company will keep Eleven's name, and Hurly, formerly Viventia's CEO, who was appointed president and CEO.

With Viventia's method, "you have a navigating front end, which is that antibody fragment, that gets to and into throughout the tumor bed better than a full-length antibody would," he said. "Then you use a cytotoxic protein payload that can kill a broad array of cancer cells – kills rapidly producing as well as quiescent cells. And supporting all of that is that it's a single protein." With ADCs, he pointed out, "you create first the antibody and then chemically conjugate the payload to it. The challenge with [such an approach] is that they come apart in circulation."

Bladder cancer occurs in three main types. Low-grade disease is a "very slow-growing, papillary tumor on the inside of the bladder," Hurly said. "You basically go into the urologist's office, you clip it away, and he says, 'I'll see you in three months.'" This type may remain chronic. Next is the worsened form, involving "carcinoma in situ, high-grade papillary tumors," he said. "You start risking systemic disease," which is the third variety, and is fatal. Viventia designed Vicinium for the second type.

Today, first-line treatment is BCG, or bacillus Calmette-Guérin immunotherapy, which involves a live attenuated strain of *Mycobacterium bovis*. This method "burns the inside lining of the wall," Hurly said, and the bacterium create a broad immune stimulation and inflammation, ideally leading to destruction of the cancer. "One of the things that's unique about high-grade bladder cancer is that complete response is all that matters," he said. "The next step [if this doesn't work] is to take the bladder out. In the last 40 years, there's not been much approved in this space at all." Valstar (valrubicin, Endo International plc), approved by the FDA for BCG-refractory disease in the fall of 1998, deploys "a very similar concept [to] BCG," he said. Data supporting the compound weren't great, and toxicities turned up. "The only real standard-of-care choice for those folks after that is bladder removal, which nobody wants to do," he said.

SYSTEMIC BID IN THE WORKS

Valstar traveled through many hands. Endo, of Dublin, gained it through the buyout of Lexington, Mass.-based Indevus Pharmaceuticals Inc., which acquired the compound by way of its $120 million takeover of Valera Pharmaceuticals Inc., of Cranbury, N.J., which in turn had bought the drug from Princeton, N.J.-based Anthra Pharmaceuticals Inc. Problems arose while Anthra still owned Valstar, but Anthra lacked resources to fix it, and sold the drug to Valera in 2006. "Patients will tell you they'll do anything they can to prevent losing their bladder and the horrible impact on the quality of life, as well as significant hospital stays." (See *BioWorld Today*, Aug. 20, 2007.)

Also in the Viventia pipeline is Proxinium, expected to enter phase II trials early next year for late-stage squamous cell carcinoma of the head and neck. Proxinium has proven generally safe and well-tolerated so far, and showed signs of anti-tumor activity. The FDA and the EMA granted

orphan drug status to the compound, and the FDA designated it as a fast track candidate. Proxinium, like Vicinium, puts EpCAM – a culprit in 80 percent of head and neck cancers – in the crosshairs. Proxinium attacks the primary tumor, Hurly said. "Almost all people die. Even those that go systemic, most of the deaths and complications are due to the primary tumor in the head and neck. These are hard, rock-solid tumors" treated first-line with chemotherapy and radiation. "Those people who stop responding really have no choice," he said. "There's just nowhere else to turn for them. They end up with major, disfiguring surgeries" that lead to a dismal quality of life and "pain that's unbearable." With Proxinium, the idea is to "treat those tumors directly, get them to soften, shrink, and hopefully go away," he said.

"I don't think any one tool in IO is going to solve all the problems," Hurly said. The checkpoint strategy represents a "nice attempt at partial responders, but they need the immune system to start its work." Viventia has efforts against systemic disease farther back in the pipeline as well. There are "lots of other efforts out there that we think we're synergistic with," he said.

In August, Eleven finalized a deal with Basel, Switzerland-based Roche AG for EGI-031, a humanized monoclonal antibody for diabetic macular edema that binds interleukin-6 (IL-6) and inhibits all known forms of IL-6 cytokine signaling. The exclusive licensing arrangement worth as much as $270 million grants Roche worldwide rights to develop and commercialize EBI-031 and all other IL-6 antagonist antibody technology owned by Eleven, which stands to collect $30 million near-term, including $7.5 million up front as the license agreement takes effect and $22.5 million as a result of the IND for EBI-031 kicking in, which happened in July. Eleven could get as much as $240 million more in regulatory, development and commercialization milestone payments, along with royalties if products are approved. EBI-031 could work also in uveitis, Eleven believes. (See *BioWorld Today*, July 11, 2016.)

In January, after Eleven disclosed mixed phase III data in severe allergic conjunctivitis with the IL-1 signaling inhibitor EBI-005 (isunakinra) – which also fizzled in the late-stage experiment for dry eye disease in May 2015 – the stock took a 77 percent hit. Leerink analyst Jason Gerberry downgraded his rating then, citing that Eleven "indicated there is no pathway forward for EBI-005, leaving preclinical stage EBI-031 as the company's lead asset." He found "no clinical data or catalysts within an investable timeframe." (See *BioWorld Today*, Jan. 20, 2016.)

Shares of Eleven (NASDAQ:EBIO) closed Wednesday at $3.50, up 13 cents, having traded as high as $4.04.