Precision Oncology News

Bolt Biotherapeutics Initiates Immunotherapy Trial of Lead Drug Candidate in HER2-Expressing Solid Tumors

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Biotech company Bolt Biotherapeutics said last Thursday that it formally kicked off the Phase I trial of its investigational immunotherapy agent BDC-1001 in patients with HER2-expressing solid tumors.

The first-in-human, open-label study will consist of both a dose-escalation and dose-expansion portion. In the dose-escalation portion, BDC-1001 will be evaluated as a monotherapy to determine the maximum tolerated dose. To be eligible for the trial, patients must have an advanced solid tumor with documented HER2 protein expression or gene amplification.

Patients in this trial will have failed standard of care or be HER2-positive but have a lower level of HER2 expression such that current HER2 therapies are either not indicated or have not been shown to be effective.

Bolt is a privately held San Francisco-based company founded in 2015 by Ed Engleman, a professor of pathology and medicine at Stanford University School of Medicine, and co-director of the Immunology and Immunotherapy Program of the Stanford Cancer Institute. The company has venture funding from Novo Holdings, Pivotal bioVenture Partners, Vivo Capital, and Nan Fund Life Sciences. Last summer, Bolt closed a series B fundraising round of $54 million. Prior to that, it raised $16 million in a series A funding round.

The raised funds will support the development of BDC-1001, an immune-stimulating antibody conjugate (ISAC) and the lead candidate in Bolt's pipeline. The molecule comprises trastuzumab attached to a toll-like receptor (TLR) 7/8 agonist payload that the biotech invented. The company refers to this novel type of molecule as a Boltbody. Bolt's supply of trastuzumab comes from an agreement with a biosimilar supplier of the antibody.

The trastuzumab antibody directs the Boltbody to the HER2-expressing tumors like a GPS navigating tool. The binding of the antibody to HER2 enables the antibody to interact with corresponding receptors on myeloid dendritic cells in the tumor microenvironment. This engagement causes the myeloid cell to engulf the tumor cell and the Boltbody ISAC. Once inside the myeloid cell, the TLR activates the myeloid

cell which allows it to trigger the priming and expansion of specialized T cells that can recognize tumor-specific neoantigens. The T cells are recruited to the tumor site, where it can destroy the cancer cells.

In pre-clinical studies conducted in Engleman's lab at Stanford University, researchers found that a TLR7 and TLR8 joint stimulator was the most potent at re-awakening myeloid cells in the tumor. Another observation that researchers made was that although the TLR agonist and a tumor-targeting antibody like trastuzumab can be administered as a combination therapy, their potency was magnified when the two molecules were conjugated together.

"There was some magic that happened that really stirred up the immune system in a very specific way to target the tumor in question," said Bolt CEO Randy Schatzman.

The fastest way to prove that the Boltbody worked was to take a known antibody that is frequently used in the clinic, such as the HER2-directed drug trastuzumab, as the tumor targeting agent and attach it to the immune-stimulating payload. The anti-HER2 ISAC treatment in pre-clinical studies shrunk and cleared tumors in animal models that had a large cancer burden and that were resistant to anti-HER2 antibody treatment.

During the recently initiated Phase I trial, BDC-1001 will be evaluated in HER2-expressing patients who have failed standard-of-care HER2-targeting therapies, such as trastuzumab or Genentech's antibody-drug conjugate ado-trastuzumab emtansine (Kadcyla). For the dose-escalation portion, investigators will monitor the drug's safety and preliminary anti-tumor activity. They will also take various biological measurements to track whether the therapy has stimulated patients' innate immune system to specifically recognize the cancer in question.

"In addition to treating patients who are resistant to standard of care, what treatment with these agents does in pre-clinical models is it leaves that host with an immune memory of its cancer. Should that cancer come back, the immune system will recognize it and eliminate it," Schatzman said. The treatment should do this even if the tumor metastasizes or alters its phenotype like changing up the types of neoantigens it expresses on the surface of the cancer cells. Because of this characteristic, Schatzman thinks the Boltbodies can even have the potential to prevent recurrence of cancer.

"We have demonstrated in some of our preclinical experiments that if a tumor loses that initial tumor antigen that we use to target the tumor with … the immune system still recognizes that tumor even without that initial antigen," said Schatzman.

Neoantigens expressed on tumor cells vary across patients. In the immune-oncology space, Schatzman noted that a number of companies are focusing on bolstering patients' innate immunity by drawing T cells to attack the cancer.

"They're targeting specific neo-antigens on the surface of tumors. They're doing high-throughput sequencing, for example, and identifying these [neo-antigens] and then using those as tags to re-train the immune system," said Schatzman. Bolt's approach with Boltbodies, he explained, would allow each patient to create an adoptive immunity to their own tumor and let the immune system choose which of these antigens it should recognize.

The important antigens, which if targeted can stop and kill tumors, can vary from person to person. "In this sense, rather than having to go through a complex personalization process that many companies are taking … we're allowing the patient's own immune system to determine what's the best way to eliminate its own cancer," said Schatzman. "We think this is a technology that can apply to many types of tumor-targeting antibodies and also to a wide variety of tumor antigens."

He added that in the preclinical pipeline, Bolt is currently working on using its technology to improve upon the efficacies of checkpoint inhibitors. The firm will name a clinical candidate sometime later this year. Additionally, the biotech has an early program targeting an undisclosed tumor antigen that may have a role in difficult-to-treat cancers, such as colorectal cancer.

Meanwhile, BDC-1001 is entering human studies as the COVID-19 pandemic has made it challenging to bring vulnerable, immunocompromised cancer patients to study sites for enrollment, treatment administration, and follow-up data collection. A number of big pharmaceutical firms have made adjustments to their clinical trials operations during the public health crisis. For example, Bristol-Myers Squibb said that for ongoing studies, no new sites will be activated until April 13, and no news studies will launch until that date as well. Pfizer is similarly pausing enrollment in new and ongoing studies for three weeks, according to multiple reports.

Bolt is continuing to recruit patients into the sites it has activated for the Phase I trial. However, the firm has also implemented measures, such as integrating home care, to limit how often patients will have to come into study sites. "So far the sites that we have initiated to conduct this trial continue to recruit and continue to operate," Schatzman said. "We're working with the [site managers and investigators] very closely to ensure the safety of our patients and yet allowing the healthcare center to do what it needs to do for other patients that require the other types of interventions" like for COVID-19.