BriaCell Codeveloping Cell-Based Cancer Therapy, Companion Diagnostic

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NEW YORK (GenomeWeb) – BriaCell Therapeutics, a clinical-stage immuno-oncology company, is slated to enter a second phase of clinical trials for a whole-cell breast cancer vaccine for which it is also codeveloping a companion diagnostic assay to identify best responders to the treatment.

BriaCell presented a poster describing the molecular profile of its vaccine, called BriaVax, at the American Association for Cancer Research annual meeting earlier this year, and shared clinical data to date in a poster at the San Antonio Breast Cancer Symposium this month.

BriaVax was initially developed by company co-founder Charles Wiseman, a physician and former director of the cancer immunotherapy laboratory at St. Vincent Medical Center in Los Angeles. The vaccine is derived from a patient with breast cancer whose chest wall lesion cells were expanded in vitro to make a breast cancer cell line.

This cell line was then stably transfected with a plasmid encoding granulocyte-macrophage colony-stimulating factor, or GM-CSF, a glycoprotein that supports dendritic cell maturation and causes tumor antigen presentation to be favored.

Prior to BriaCell's founding in 2014, two clinical trials of the vaccine were run. One, which established safety, used the parental cell line that did not contain the GM-CSF and treated 14 patients. The second trial involved four patients and the cell line expressing the GM-CSF plasmid, now called BriaVax.

In this trial, three patients had breast cancer and one had ovarian cancer. One of the breast cancer patients showed a strong response to the vaccine.

"This was a person who had metastatic breast cancer ... she was treated with BriaVax in a couple cycles, and her tumors regressed," Markus Lacher, BriaCell's senior director of research and development said in an interview.

As described in a 2006 journal article, regression included not just primary tumors in the breast, but also metastatic lung lesions that regressed totally.

After this US Food and Drug Administration-approved phase I trial, the patient's treatment ended, her tumors recurred, and metastases were also detected in the brain. Wiseman managed to get FDA approval to retreat her, and she again responded to continued treatment with BriaVax. In fact, although the brain is thought to be a protected site not susceptible to immunotherapy, multiple brain metastases did regress after only three inoculations.

"That was very intriguing from all sorts of points of view, [and] it justified the build-up of a company around the whole program," Lacher said. Although the patient died about 10 years

ago, in 2014 Wiseman was able to get everything in place for building a company and restarting the clinical trials.

Now, BriaCell plans to initiate the next wave of clinical trials and dose the first new patient starting in 2017. The protocol involves an initial pretreatment with cyclophosphamide at low, subclinical doses to help get rid of suppressor T cells as well as alpha-interferon injections after vaccine administration. The vaccine is also irradiated to make it replication incompetent.

This latter aspect of the protocol currently limits the distance that the live vaccine can travel. Thus, the first trials will be conducted at a clinic in Santa Rosa, California, about two hours away from the manufacturing site at the UC Davis GMP facility in Sacramento.

In the future, however, the firm plans to enroll other sites as well, and is also considering changing the formulation so that it can ship to other centers all over the world in a cryopreserved state.

Although companion diagnostics are often developed subsequent to clinical trials, to narrow the treated population to those most likely to benefit, BriaCell plans to codevelop a companion test as the clinical trials are ongoing. To this end, the firm has filed provisonal US patent applications on a companion diagnostic test, called BriaDx, to pair with the vaccine. The final format of the companion test is not set in stone, Lacher said, but the firm has some leads from the original successful patient trial.

For example, the patient who responded to the vaccine had a match with BriaVax at a class I HLA allele and a class II HLA allele.

"This is to some extent surprising because BriaVax is a breast cancer cell line, so it's not like an antigen-presenting cell that you would expect expresses class II HLA," Lacher said. Allele matches on both class I and class II HLA suggests to the firm that BriaVax can potentially act as an antigen-presenting cell, "so that the patient's T cells could directly recognize the vaccine and antigens that it expresses from BriaVax," Lacher said.

"If you can imagine that you have antigens that are co-expressed in the tumor and in BriaVax, and they're presented on the cell surface of BriaVax and recognized by the T cells, you can envision how a T cell gets very excited and could also move on to attack the tumor," he added.

The vaccine also expresses several other factors known to stimulate an immune response, Lacher said. And levels of soluble CD40 ligand in the patient's blood serum were also elevated during each of the treatment phases, which could suggest further avenues for CDx development.

The company has also performed microarray profiling of BriaVax itself and discovered factors that encode tumor-associated antigens, Lacher said. It found other hints based on analyses of publicly available datasets, comparing BriaVax expression data with other cell types.

During the clinical trial, which expects to enroll up to 24 advanced stage breast cancer patients, BriaCell plans to collect blood plasma and serum, as well as urine, and tissue biopsies when feasible, to assess factors that correlate with treatment response using "substantial multiplex screens" and cell-based assays using technologies like ELISPOT, T-cell proliferation assays, or flow cytometry, Lacher said.

These might include a molecular component, provided tissue biopsy material is available, although Lacher noted that the priority would be to have a high-sensitivity and -specificity diagnostic test that works exclusively with blood or urine.

"Hopefully, once we have several patients treated, we can confirm or adjust our hypotheses on how the companion diagnostic should look," Lacher said..