BriaCell Therapeutics Corp. (TSXV: BCT) - $0.17 / Share

The Case For Investment In BriaCell Therapeutics

Earlier this week, BriaCell Therapeutics Corp. (TSXV: BCT.V) announced the company is making progress towards the initiation of a Phase 1/2a clinical study with BriaVax™, a proprietary allogeneic whole tumor cell vaccine for the treatment of late-stage breast cancer. Specifically, management has submitted a Chemistry, Manufacturing, and Controls (CMC) amendment that includes the details of extensive testing performed on BriaVax. This is one of the final steps prior to U.S. FDA authorization to begin the study.

BriaCell is one of my favorite under-the-radar micro-cap immuno-oncology stories. Previous clinical data on BriaVax has been highly encouraging, including published results from a case study in which a 58-year old woman with recurrent late stage metastatic breast cancer achieved complete remission of lung lesions and near-complete remission of multiple breast lesions following treatment with an earlier version of the therapeutic vaccine (Wiseman & Kharazi, 2006).

BriaCell aims to begin the Phase 1/2a study in March 2017. Management has already appointed the lead principal investigator for the study, Dr. Jarrod P. Holmes. Dr. Holmes is a Board Certified Oncologist and a leading expert in breast cancer vaccines at Annadel Medical Group and St. Joseph Health-Sonoma County, CA. Separately, the company also announced that Cancer Insight, LLC, led by Dr. George Peoples, a surgical oncologist and leading expert in breast cancer vaccines, with serve as the contract research organization (CRO) to conduct the trial. A separate CRO, Biologics Consulting will handle regulatory affairs.

Below is a quick update on the story, along with my investment thesis for the stock.

Quick Refresher on BriaVax

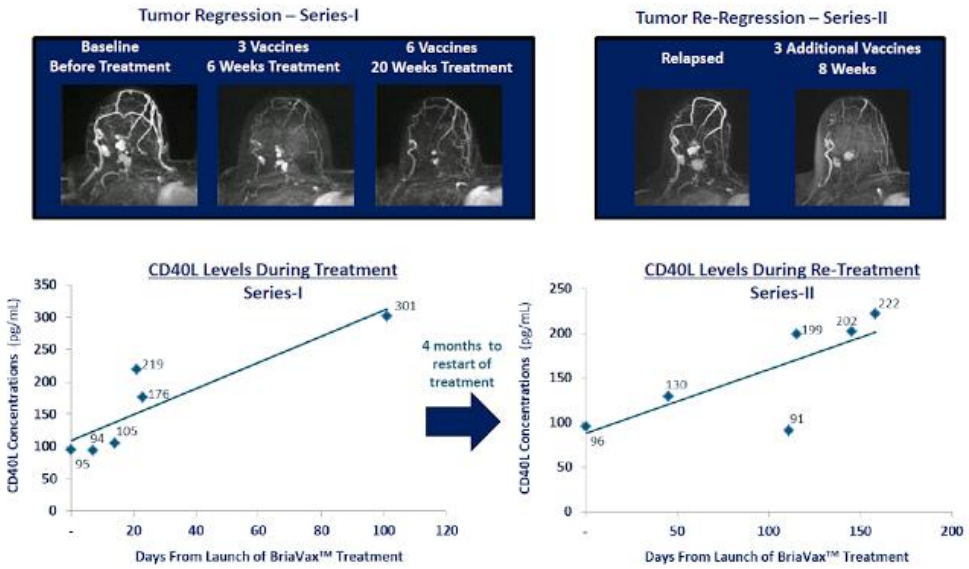
BriaVax™ is a proprietary allogeneic whole tumor cell vaccine isolated from a chest wall lesion of a 39-year-old woman with metastatic breast cancer. The irradiated cells are ER/PR negative and overexpress HER-2/neu, a clinically validated target of effective monoclonal antibody therapeutics. BriaVax has been genetically engineered to release sargramostim (granulocyte macrophage - colony-stimulating factor [GM-CSF]) for up-regulation of professional antigen-presenting cells. GM-CSF has been shown to be the most potent immunostimulatory secreted molecule for inducing tumor immunity (1) and is believed to provide an antitumor effect that prolongs survival and disease-free survival in subjects with stage III and IV melanoma (2) and metastatic non-small cell lung cancer (3). Also, part of the treatment regimen is the addition of low-dose cyclophosphamide (CY) prior to inoculation to down-regulate the activity of regulatory T cells and the use of interferon (IFN) alpha following inoculation to boost differentiation of dendritic cells.

Treatment with BriaVax is the result of decades of clinical investigation and research into therapeutic cancer vaccines and the use of an allogeneic whole cell breast tumor line that overexpresses clinically validated tumor antigens. The cells have been genetically engineered to secrete GM-CSF, which has multiple effects on the tumor-immune response equilibrium, including activating dendritic cell recruitment and maturation. The protocol employs a novel use of CY to take the "foot off the brake" with respect to regulatory T cell response and then follows with a local injection of IFN-alpha to "step on the gas" and evoke prolonged immune response.

- BriaVax Mechanism of Action -

In addition to stimulating anti-tumor immunity, BriaVax is believed to work by increasing expression of CD40 Ligand (CD40L), a costimulatory protein found on antigen presenting cells, such as T cell, B cell, and natural killer (NK) cells, that is required for their activation (4). Activation of CD40L has a variety of downstream effects, including dendritic cell maturation and an increase in serum levels of CD4+, CD8+, and NK cells known for their anti-tumor activities (5). BriaCell has shown that CD40L levels increase following the administration of BriaVax, with one subject demonstrating tumor regression.

Hypothetical Mechanism of Action



- Predictors of Response -

BriaCell believes that they have identified a gene signature predictive of response to BriaVax. For example, following the successful completion of the second Phase 1 study (n=4) (6), the scientists at BriaCell observed potentially prolonged overall survival among three of the four patients (median OS: ~35 months); in addition, one patient, with an OS of 33.7 months, demonstrated clinically significant (>90%) tumor) regression.

Focusing more closely on these patients, BriaCell conducted a molecular analysis of both the BriaVax cell line and blood cells obtained from patients in the Phase 1 study. This "gene signature" analysis informed the company about a putative BriaVax mechanism of action and paved the way for the development of a potential companion diagnostic for both patient selection as well as monitoring during human clinical trials. For example, the one patients (subject A002) noted above who demonstrated clinically significant tumor regression shared both MHC class I (HLA-A) and class II (HLA-DRB3) alleles with BriaVax.

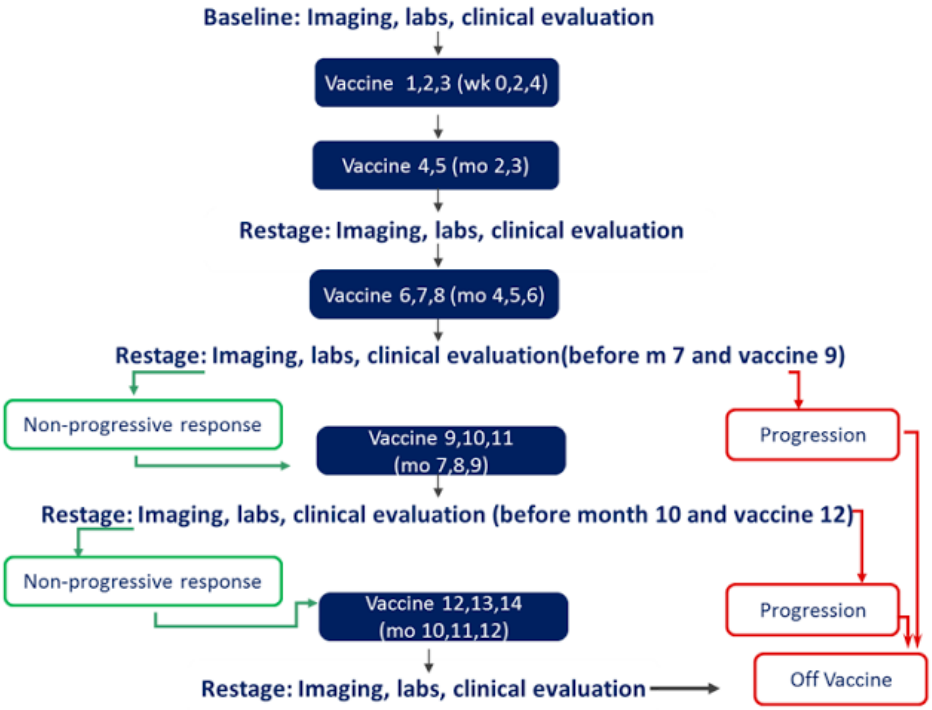
Subject ID	Tumor Type	Survival (months)	Tumor regression	HLA-A		HLA-B		HLA-DRB3	
A001	Breast	40.7	No	02:01	24:02	13:02	41:01	03:01	-
A002	Breast	33.7	Yes	02:01	11:01	18:03	44:02	02:02	-
A003	Ovarian	35.6	No	02:01	03:01	07:02	13:02	Negative	-
B001	Breast	7.0	No	11:01	-	35:01	40:01	Negative	-
BriaVax	Breast	N/A	N/A	11:01	24:02	35:08	55:01	01:01	02:02

The basic findings, which were presented at AACR in April 2016 (Poster #2369), show that BriaVax expresses several genes known to encode tumor-associated antigens, such as PRAME, a Cancer / Testis Antigen (CTA), which in combination with immune stimulatory factors including HLA class I and II components, are hypothesized to result in activation of tumor-specific T cells via mechanisms of direct antigen presentation, cross-presentation, and/or cross-dressing. PRAME is expressed in 88% of primary melanomas (7) and is a marker of poor prognosis in breast cancer (8, 9). Other human malignancies that express PRAME include acute and chronic leukemias, medulloblastoma, lung cancer, head and neck cancer, renal carcinoma, and multiple myeloma.

Based on analysis of BriaVax specific alleles and HLA matching frequencies for various ethnic groups, management believes that 60% of all breast cancer patients will match at least one allele, with 20% matching both alleles. Recall, the uber-responder noted above matched both alleles and achieved near-complete remission. In the future, it might make sense for BriaCell to manufacture varying versions of BriaVax with each HLA class I and II alleles, thus creating perhaps the most effective personalized breast cancer therapeutic options available to all patients with disease.

The Planned Phase 1/2a Program

BriaCell expects to initiate a Phase 1/2a program with BriaVax in March 2017. The trial is expected to enroll up to 24 late-stage cancer patients with metastatic breast cancer who have failed at least one line of prior therapy. Enrollment is expected to take place at several experienced clinical sites in the U.S. Below is a schematic of the planned protocol, although management is in discussion with the U.S. FDA about amending the trial to allow for dose ranging, and is planning a roll-over protocol so that patients who do not respond to BriaVax can continue treatment in combination with an immune checkpoint inhibitor.



Looking At The BriaVax Market Opportunity

According to epidemiology data published in the *Journal of the National Cancer Institute* in 2013, approximately 80% of estimated 2.8 million breast cancer patients in the U.S. each year present with invasive disease. That equates to approximately 2.2 million cases. Roughly one-quarter of these will metastasize and 20% will fail first-line therapy and be eligible for treatment with a therapeutic candidate like BriaVax. That equates to approximately 100,000 patients per year (10).

If we conservatively assume that only the 20% that match both BriaVax alleles receive the drug (~20,000 patients) and that management can capture 25% market share, the likely peak penetration for BriaVax is 5,000 patients under the most conservative base case. Priced at $48,000 per course of treatment (6 vaccines), the estimated peak sales of BriaVax is $250 million. A more aggressive assumption that 60% of the patients that match at least one HLA allele may try BriaVax expands the peak sales number to $1 billion. Keep in mind, I think it makes sense for BriaCell to manufacture cells lines with varying HLA alleles, thus potentially targeting 100% of the eligible market.

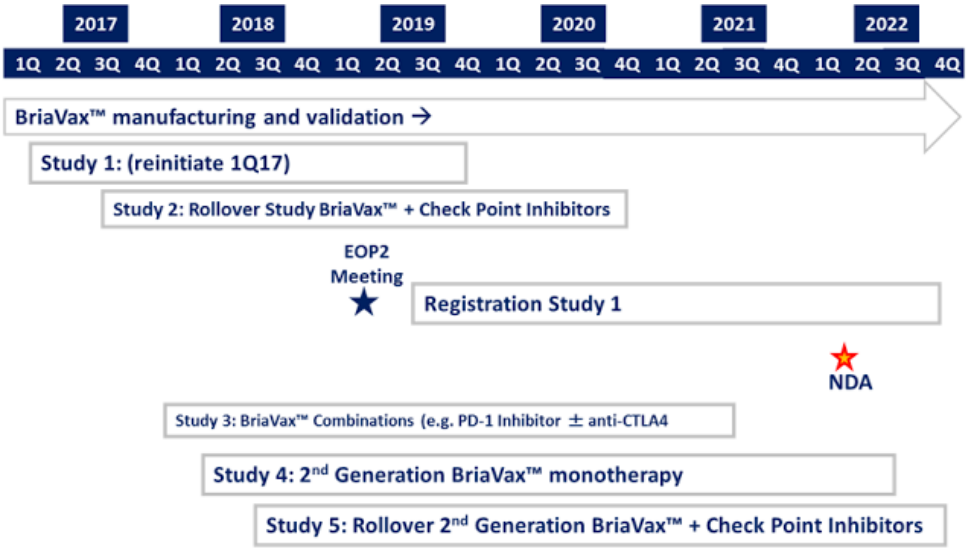
The company is also looking at the potential to use BriaVax in combination with other treatment options, such as checkpoint inhibitors, looking for an additive or synergistic effect. This is a logical path for BriaCell because checkpoint inhibitors (such as PD-1, PD-L1, CTLA4) eliminate immunosuppression that should improve the efficacy of BriaVax. The combination with immunostimulatory antibodies (GITR, OX40) should also enhance response to BriaVax.

Improved response may move BriaVax from second-line to first-line therapy. This is where the numbers start to get really large because the first-line market is 4X the size of the second-line market. Peak sales of BriaVax could be $1 billion (conservative HLA matching criteria) to $4 billion (more liberal HLA matching criteria). First-line patients may also live longer than second-line patients, potentially expanding the number of BriaVax vaccines beyond the six being tested in the planned Phase 1/2a study noted above. Of course, all this is only just in breast cancer!

The BriaCell Investment Thesis

What I find most interesting about BriaVax is the potential for a potent targeted approach to immunotherapy. BriaVax is interesting because the administration of a genetically engineered whole tumor cell vaccine has the potential to present multiple tumor-specific antigens to the immune system, stimulating dendritic cells and inducing a humoral response. The biomarker and gene expression data presented at AACR in April 2016 significantly improves the likelihood of response based on the double matching of HLA alleles (approx. 20% of all breast cancer patients). BriaCell is working on a companion diagnostic, BriaDx™, to prospectively identify patients most likely to respond to BriaVax.

BriaCell has an aggressive development plan in place for BriaVax. The Phase 1/2a second-line therapy should start in March 2017. A second Phase 2 study examining BriaVax in combination with checkpoint inhibitors is also planned for 2017. As noted above, there is a logical scientific rationale for a synergistic effect. Combination therapy has the potential to expand the peak sales opportunity of BriaVax from $250 million (conservatively) to $1 billion (conservatively) given the move to first-line therapy. More aggressive use of BriaVax, expanding the HLA allele profile through various cell lines, or expansion into other solid or hematologic tumors creates additional upside to these forecasts.



BriaCell held $2.2 million in cash as of October 31, 2016. The estimated cost of the planned Phase 1/2a study along with funding operations over the next six months should be covered by this level; however, if BriaCell wants to expand the program into a first-line combination therapy study, as well as develop the companion diagnostic platform known as BriaDx™, additional funds will be necessary.

That being said, I'm not overly concerned with the lack of cash at this stage. I think BriaVax is incredibly intriguing and with a current market capitalization (USD) of only $17 million, BriaCell looks like a very interesting "lotto play" given my belief that BriaVax peak sales ranges somewhere between $250 million (conservative) to $4 billion (aggressive). Below is a look at the valuation of BriaCell compared to some similar-stage immuno-oncology peers. BriaCell certainly looks undervalued based on market potential and peer-valuation analysis.

Company	Therapeutic Area	Development Stage	Breast Cancer	Market Cap
Xencor Inc - XNCR	Vaccines / Immuno-Oncology	Phase 2		$975.9
Loxo Oncology - LOXO	Immuno-Oncology	Phase 2	Yes	$895.8
Ziopharma Oncology - ZIOP	Immuno-Oncology	Phase 2	Yes	$866.8
Inovio - INO	Vaccines	Phase 2	Yes	$473.2
Celldex Therapeutics - CLDX	Immuno-Oncology	Phase 2	Yes	$348.3
VBI Vaccines - VBIV	Vaccines / Immuno-Oncology	Phase 1		$134.0
Immune Design - IMDZ	Immuno-Oncology	Phase 2	Yes	$132.1
Cascadian Therapeutics - CASC	Vaccines	Phase 2	Yes	$97.5
Immunovaccine - IMV.TO	Immuno-Oncology	Phase 2		$54.7
Del Mar Pharma - DMPI	Immuno-Oncology	Phase 2		$50.1
TapImmune Inc. - TPIV	Immuno-Oncology	Phase 1/2	Yes	$36.2
Regen BioPharma - RGBP	Immuno-Oncology	Phase 1/2	Yes	$8.7
			Average	$339.4
BriaCell Therapeutics - BCT.V	Immuno-Oncology	Phase 1/2	Yes	$17.1

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Conclusion

BriaCell Therapeutics remains one of my favorite under-the-radar immuno-oncology names. Therapeutic cancer vaccines have a lamentable history, but the science has come a long way since the failures of Dendreon's Provenge®. BriaVax is an allogeneic whole cell vaccine, and thus not hampered by the immune masking or the logistical commercial nightmares of previous autologous approaches. Instead, BriaVax seems to offer the ideal immunotherapy - powerful enough to induce both a broad-scale innate and adaptive immune reaction, targeted to reduce systemic side-effects, and personalized based on genetic biomarkers to improve the odds of success.

There is also a strong scientific rationale for a combination of BriaVax with checkpoint inhibitors and expansion of the program into additional solid tumors or hematologic malignancies. Management looks solid (I've met and spoken to them many times) and the company's development plan is sound. Finally, large pharmaceutical partners are sure to come calling if the current Phase 1/2a study is successful.
