SVBR-1-GM is a whole-cell GM-CSF expressing targeted immunotherapy prepared from a breast cancer cell line (derived from a grade II tumor) grown from breast cancer cells expressing multiple HLA class II antigens. Higher disease control rates have been noted with patients grade I or II tumors compared to Grade III tumors.

In an initial, pilot Phase I clinical trial with 4 evaluated subjects, one “Special Responders” experienced prompt, widespread proliferation of PBMCs at multiple sites of metastatic breast cancer (Wiseeman and Khani, 2006; The Breast Journal; Volume 12 Number 5, 2006 475-486).

In a completed Phase IIa clinical trial for advanced breast cancer (ClinicalTrials.gov NCT03306942) with 23 subjects dosed with SVBR-1-GM, tumor regression was noted in 3 subjects at matching with SVBR-1-GM at least at one HLA allele. The clinical benefit for Grade I/II patients with immune responses (DTH) was 87% (71%).

In an ongoing Phase IIb clinical trial for advanced breast cancer lasting SVBR-1-GM in combination with a PD-1 inhibitor pembrolizumab (Keytruda; Merck or IMC-A120; Incyte/Macrogen) (ClinicalTrials.gov NCT03328026), 11 subjects have thus far been dosed. All 3 patients with Grade I/II tumors had disease control (100%).

Mechanism of Action (MoA): SVBR-1-GM acts as an antigen-presenting cell for primed T cells (Lachter et al. 2018; T-cell Immunotherapeutics, 2018). T cells, which can mediate higher tendency to PBMCs proliferation in response to Actin (GM-CSF, IL-2, IL-21) – following stimulation with HER2 and PEMF peptides. Different soluble cytokine levels were observed (CD40L, MCP-1, IL-1RA) in 5 patients. Increased antibody levels compared to baseline were observed in 6 of the 12 patients assessed. Patients with objective tumor regression had the most pronounced responses. In the combination therapy study, 2 patients have shown objective evidence of tumor regression, including one patient with liver metastases, which decreased by 25%, and one patient with adrenal and dorsal metastases (29% reduction in target lesion). Both patients had Grade II tumors, similar to the tumor from which SVBR-1-GM was derived.

These observations confirm the ability of the SVBR-1-GM regimen to elicit regression of far advanced refractory metastatic breast cancer. No serious toxicities clearly attributed to the SVBR-1-GM regimen were observed. Pharmacodynamic analysis of humoral and cellular immune response showed notable upregulation, the strongest responses being seen in those with measurable clinical regression. Patients with Grade I or II tumors appeared more likely to respond.

SVBR-1-GM is a GM-CSF secreting breast cancer cell line that also expresses HLA class I & II antigens. Irradiated SVBR-1-GM is used in a regimen including pre-dose low-dose cyclophosphamide and post-dose local interferon-β2b. The SVBR-1-GM regimen has been used alone (“Monotherapy” study ClinicalTrials.gov NCT03306947) and in combination with immune checkpoint inhibtors (ongoing combination clinical trial ClinicalTrials.gov identifier NCT03328026). Here we report regression of metastatic breast cancer with pharmacodynamic analysis with immune expressions.

23 patients with advanced breast cancer refractory to standard therapies were treated with the SVBR-1-GM regimen in the monotherapy trial with cycles every 2 weeks for the first month and then monthly. The combination study is evaluating the SVBR-1-GM regimen with checkpoint inhibitors (PD-1 inhibitors pembrolizumab or ICMA/00012) with cycles every 3 weeks (15 patients have been dosed to date). Pharmacodynamic analysis includes delayed type hypersensitivity (DTH), antibodies against SVBR-1 (precursor of SVBR-1-GM), blood lymphocyte proliferation (determined using flow cytometry), circulating cytokine analysis, and proteomic analysis (Luminex based assays) following stimulation with peptides of antigens in SVBR-1-GM cells (HER2 and PRAME).

In the monotherapy study, tumor regression was seen in 3 patients. 21 patients developed measurable DTH signaling collagen type IV. In the combination regimen the treatment showed increased proliferation and cytokine secretion (GM-CSF, IL-2, IL-21) followed stimulation with HER2 and PEMF peptides. Different soluble cytokine levels were observed (CD40L, MCP-1, IL-1RA) in 5 patients. Increased antibody levels compared to baseline were observed in 6 of the 12 patients assessed. Patients with objective tumor regression had the most pronounced responses. In the combination therapy study, 2 patients have shown objective evidence of tumor regression, including one patient with liver metastases, which decreased by 25%, and one patient with adrenal and dorsal metastases (29% reduction in target lesion). Both patients had Grade II tumors, similar to the tumor from which SVBR-1-GM was derived.

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**CONCLUSIONS AND HYPOTHESES**

The SVBR-1-GM regimen +/- pembrolizumab is able to induce an effective immune response and tumor regression in advanced breast cancer patients.

- Patients with grade I (well-differentiated) or grade II (moderately differentiated) tumors are more likely to respond with tumor regression and disease control.
- A more robust immune response appears to occur in patients who respond to treatment with tumor regression compared to those who do not.

Clinical and pharmacodynamic responses to the modified whole cell immune-modulator in patients with advanced breast cancer from two phase I/II trials

Vivekananda G. Sunkari¹, Jacqueline Galeas³, Shaker R. Dakhil³, Jarrod Holmes³, Saveri Bhattacharya³, Carmen J. Califf³, Aley Kundra³, Daniel L. Adams³, Diane DaSilva³, George E. Peoples³, Charles L. Wiseman⁴, William Y. Williams⁵, and Markus D. Lachter⁴

¹BriaCell Therapeutics Corporation, Berkeley, CA; ²Cancer Center of Kansas, KS; ³St. Joseph Health Santa Rosa, Santa Rosa, CA; ⁴Thomas Jefferson University, Philadelphia, PA; ⁵University of Miami Health, Miami, FL: The Everett Clinic, Everett, WA; ⁶Creat Micro Tech, Rockville, MD; University of Southern California, Los Angeles, CA; ⁷Cancer Insight LLC, San Antonio, TX

References: V. Sunkari et al. (2020), V.V. Williams et al. (2021). MD Lachter (mlachter@briacell.com)