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Clinical and pharmacodynamic responses to a modified whole tumor cell immunotherapy in patients with advanced breast cancer from two phase I-IIa trials

Vivekananda G. Sunkari[1], Jacqueline Galeas[1], Shaker R. Dakhil[2], Jarrod Holmes[3], Saveri Bhattacharya[4], Carmen J. Calfa[5], Ajay Kundra[6], Daniel L. Adams[7], Diane DaSilva[8], George E. Peoples[9], Charles L. Wiseman[1], William V. Williams[1], and Markus D. Lacher[1].

[1]BriaCell Therapeutics Corporation, Berkeley, CA; [2]Cancer Center of Kansas, KS; [3]St. Joseph Health Santa Rosa, Santa Rosa, CA; [4]Thomas Jefferson University, Philadelphia, PA; [5]University of Miami Health, Miami, FL; [6]The Everett Clinic, Everett, WA; [7]Creatv MicroTech, Rockville, MD; [8]University of Southern California, Los Angeles, CA; [9]Cancer Insight LLC, San Antonio, TX

Contacts: VG Sunkari (vivek@briacell.com), WV Williams (williams@briacell.com), MD Lacher (mlacher@briacell.com)

ABSTRACT

SV-BR-1-GM is a GM-CSF secreting breast cancer cell line that also expresses HLA class I & II antigens. Irradiated SV-BR-1-GM is used in a regimen including pre-dose low-dose cyclophosphamide and post-dose local interferon-α2b. The SV-BR-1-GM regimen has been used alone ("Monotherapy" study ClinicalTrials.gov NCT03066947) and in combination with immune checkpoint inhibitors (ongoing combination study ClinicalTrials.gov identifier NCT03328026). Here we report regression of metastatic breast cancer and pharmacodynamic analysis with immunologic correlates.

23 patients with advanced breast cancer refractory to standard therapies were treated with the SV-BR-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 SV-BR-1-GM regimen with checkpoint inhibitors (PD-1 inhibitors pembrolizumab or INCMGA00012) with cycles every 3 weeks (11 patients have been dosed to date). Pharmacodynamic analyses include delayed-type hypersensitivity (DTH), antibodies against SV-BR-1 (precursor of SV-BR-1-GM), blood lymphocyte proliferation (determined using flow cytometry), circulating cytokines in sera and cytokine secretion (Luminex based assays) following stimulation with peptides of antigens expressed in SV-BR-1-GM cells (HER2 and PRAME).

In the monotherapy study, tumor regression was seen in 3 patients. 21 patients developed measurable DTH signifying cellular immunity. Blood lymphocytes from responders after treatment showed increased proliferation and cytokine secretion (GM-CSF, IL-2, IL-21) - following stimulation with HER2 and PRAME peptides. Differential serum 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 dural metastases (29% reduction in target lesion). Both patients had Grade II tumors, similar to the tumor from which SV-BR-1-GM was derived.

These observations confirm the ability of the SV-BR-1-GM regimen to elicit regression of far advanced refractory metastatic breast cancer. No serious toxicities clearly attributed to the SV-BR-1-GM regimen were observed. Pharmacodynamic analysis of humoral and cell-mediated immune responses 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.

BACKGROUND

- SV-BR-1-GM is a whole-cell, GM-CSF expressing targeted immunotherapy prepared from a breast cancer cell line (derived from a grade II tumor) with features of antigen-presenting cells including HLA class II expression.
- Higher disease control rates have been noted for patients with Grade I or II tumors compared to Grade III tumors.
- In an **initial, pilot Phase I** clinical trial with 4 evaluable subjects, one "Special Responder" experienced prompt, widespread regression at multiple sites of metastatic breast cancer (Wiseman and Kharazi, 2006; The Breast Journal, Volume 12 Number 5, 2006 475– 480).
- In a **completed Phase I/IIa** clinical trial for advanced breast cancer (ClinicalTrials.gov NCT03066947) with 23 subjects dosed with SV-BR-1-GM, tumor regression was noted in 3 subjects, all matching with SV-BR-1-GM at least at one HLA allele. The clinical benefit rate for Grade I/II patients with immune responses (DTH) was 5/7 (71%).
- In an **ongoing Phase I/IIa** clinical trial for advanced breast cancer testing SV-BR-1-GM **in combination with a PD-1 inhibitor** (pembrolizumab/Keytruda, Merck; or INCMGA00012, Incyte/Macrogenics) (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)

SV-BR-1-GM acts as an antigen-presenting cell for primed T cells (Lacher *et al.*, Front Immunol. 2018 May 15;9:776 and **Figure 1**).

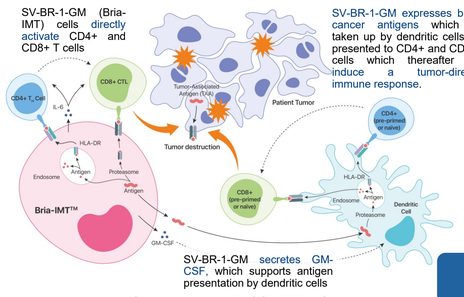

Figure 1. Model of Proposed MoA of SV-BR-1-GM

METHODS

Patient Treatment

- **The SV-BR-1-GM Regimen:**
  - Pre-dose cyclophosphamide (300 mg/m^2) 2-3 days prior to SV-BR-1-GM inoculation.
  - DTH skin test with ~1 million cells (forearm), then inoculation of **~20**-50 million irradiated SV-BR-1-GM cells intradermally, split into 4 inoculations (x2 upper back, x2 thighs).
  - Interferon-α2b intradermally (10,000 IU in each inoculation site) 2±1 and 4±1 days following SV-BR-1-GM inoculation.
  - NCT03328026 only: Pembrolizumab (Keytruda; 200 mg IV) or INCMGA00012 (375 mg IV) during one of the IFN-α2b visits.
- **Cycles:**
  - NCT03066947 ("monotherapy"): Treatment is performed every 2 weeks for the first month and then every month.
  - NCT03328026 (with pembrolizumab or INCMGA00012): Treatment every 3 weeks.

RESULTS

Patient Characteristics (23 total)	No HLA Allele Matches (n=6)	1+ HLA Allele Matches (n=17)	2+ HLA Allele Matches (n=5)	All Patients (n=23)
Age	55 ± 14	60 ± 8	68 ± 7	59 ± 10
Median Prior Systemic Regimens	5.5 (range 2-13)	4 (range 0-10)	3.5 (range 3-7)	5 (range 1-13)
% ER/PR +	67%	47%	67%	52%
% Her2/neu +	17%	20%	33%	19%
% Triple Negative	33%	40%	0%	38%
Grade I/II	2	4	2	6
Grade III	4	13	3	17

Patient Characteristics (11 total)	No HLA Allele Matches (n=4)	1+ HLA Allele Matches (n=7)	2+ HLA Allele Matches (n=5)	All Patients (n=11)
Age	61 ± 11	62 ± 9	62 ± 12	62 ± 9
Median Prior Systemic Regimens	6 (range 2-10)	4 (range 1-14)	4 (range 1-14)	4 (range 1-14)
% ER+ or PR +	75%	67%	50%	70%
% Her2/neu +	50%	50%	50%	50%
% Triple Negative	0%	0%	0%	0%
Grade I/II	1	2	1	3
Grade III	3	4	3	7

Table 1. Patient Characteristics from the "Monotherapy" Study (Top) and the PD-1 Inhibitor Combination Study (Bottom). Note that only one patient (in the monotherapy study) with a grade III tumor showed evidence of tumor regression, whereas 2 patients with grade I or II tumors had tumor regressions. **The patients were all heavily pretreated having failed multiple prior regimens.**

RESULTS

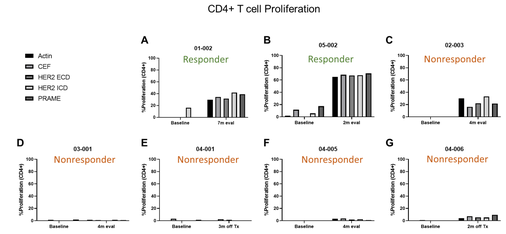

Figure 2. Increased CD4+ T cell proliferation following treatment with the SV-BR-1-GM Regimen in Responders (presented similarly at AACR 2019). SV-BR-1-GM expresses the cancer/testis antigen PRAME and HER2 (ERBB2). Patient PBMCs were stimulated with overlapping sets of PRAME and HER2 peptides. T cell proliferation was assessed via CellTracer, a fluorescent dye with diminishing fluorescence following cell division. **Substantially higher percentages of PRAME and HER2-specific CD4+ T cells at post-Rx compared to baseline time points for responders (tumor regression) compared to non-responders.** However, PBMCs of responders also demonstrated increased proliferation when stimulated with negative control (Actin) and positive control (viral antigens; CEF) peptides, **suggesting that responders have a higher tendency to develop T cell proliferative responses *per se*** compared to nonresponders.

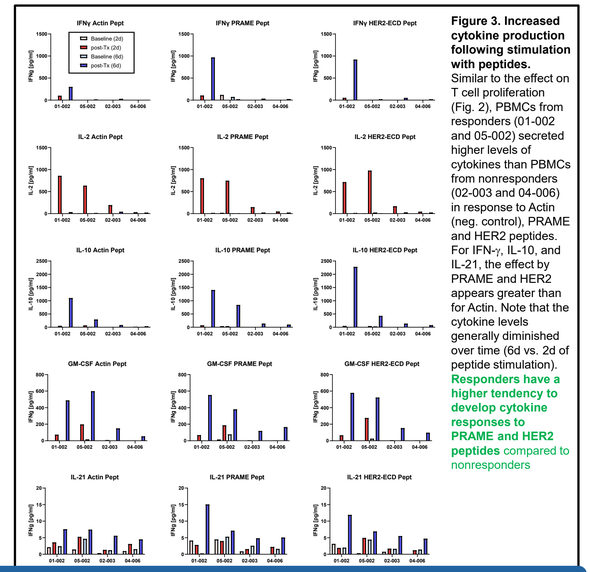

Figure 3. Increased cytokine production following stimulation with peptides. Similar to the effect on T cell proliferation (Fig. 2), PBMCs from responders (01-002 and 05-002) secreted higher levels of cytokines than PBMCs from nonresponders (02-003 and 04-006) in response to Actin (neg. control), PRAME and HER2 peptides. For IFN-γ, IL-10, and IL-21, the effect by PRAME and HER2 appears greater than for Actin. Note that the cytokine levels generally diminished over time (6d vs. 2d of peptide stimulation). **Responders have a higher tendency to develop cytokine responses to PRAME and HER2 peptides** compared to nonresponders

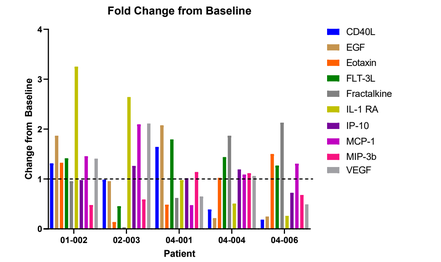

Figure 4. Circulating Cytokine Increase from Baseline
Shown are fold-change increases of circulating cytokine levels. Only Patient 01-002 had significant tumor reduction in this group of patients.
Each patient presents with a unique cytokine response profile.

Patient Characteristics	Monotherapy Study (n=6)	Pembrolizumab Combo Study (n=3)	All Patients (n=8)[1]
Age	65 ± 7 (median 64)	67 ± 7 (median 70)	65 ± 7 (median 64)
Median Prior Regimens	5 (range 0-13)	10 (range 9-12)	7 (range 0-13)
% ER/PR +	80%	100%	86%
% Her2/neu +	0%	33%	14%
% Triple Negative	20%	0%	14%
Grade I	1	0	1
Grade II	5	3	7
Immune Responders*	5	3	7
Disease Control	**67%**	**100%**	**75%**
Disease Control in Immune Responders[2]	**80%**	**100%**	**86%**

Table 2. Patients with Grade I or II tumors were more likely to show disease control (including partial response and stable disease).
*Immune responders were those able to mount a delayed-type hypersensitivity (DTH) response.
[1]One patient was in both the monotherapy study and the combination therapy study
[2]One patient in the monotherapy was unable to develop a DTH response to any of the inoculations

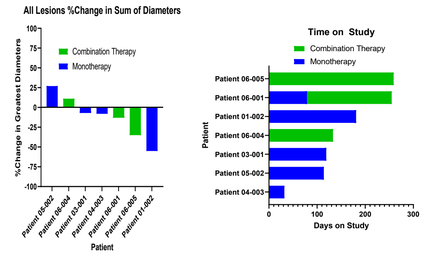

Figure 5. Changes in Tumor Burden (Left) and Time on Study (right) for Grade I/II Patients
Patients from the monotherapy study are in blue and from the combination study in green. One patient (06-001) was on both studies
Patients with grade I/II tumors showed reductions in tumor burden and were able to stay on study

CONCLUSIONS AND HYPOTHESES

- **The SV-BR-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.**