SV-BR-1-GM, a Whole-Cell Targeted Immunotherapy for Breast Cancer: Preliminary Clinical Data

Jarrod P. Holmes, M.D.[1], Elizabeth Tan-Chiu, M.D.[2], Charles L. Wiseman, M.D.[4], Markus D. Lacher, Ph.D.[4] , George Peoples, M.D.[3], William V. Williams, M.D.[4]*

[1]Saint Joseph Heritage Healthcare, Santa Rosa, CA; [2]Florida Cancer Care, Plantation, FL; [3]Cancer Insight LLC, San Antonio TX; and [4]BriaCell Therapeutics Corp., Berkeley, CA*presenting author

BriaCell THERAPEUTICS CORP.

#10970

ABSTRACT

BACKGROUND/METHODS: SV-BR-1-GM is a GM-CSF transfected breast cancer cell line which expresses HLA class I & II antigens. SV-BR-1 GM was used in 4 evaluable patients in a previous clinical trial together with low-dose cyclophosphamide 2-3d prior to ID injection of SV-BR-1-GM ($20x10^6$ cells divided into 4 sites) and interferon-α into the inoculation sites ~2 & 4 days subsequently. Cycles were q2 weeks x3 then q mo x 3 (Breast J. 2006;12(5):475-80). A partial response of widely metastatic breast cancer was seen in a patient who matched SV-BR-1-GM at HLA-DRB3*02:02.

RESULTS: This regimen is being used in clinical trial NCT03066947 in St IV breast cancer. Six patients have been inoculated (Table). Tumor regression was seen in 2 patients. 01-002 presented with liver, bone and 20 classic miliary lung metastases (up to 9mm). This subject previously failed 7 chemo regimens. She matched SV-BR-1-GM at Class I & II HLA loci. Imaging at 3 mo showed virtually complete regression of all 20 identifiable lesions in the lungs. This response was maintained at 6 mo. but the subject was taken off protocol because of disease progression in the liver and bone. 01-005, matching HLA-A*24:02, had notable regression of cutaneous lesions, but developed worsening pleural and pericardial effusions and irreversible cardiac arrest (unlikely related). 02-004 with inflammatory breast cancer withdrew due to worsening breast inflammation. Treatment was generally well-tolerated: local injection-site irritation was the most common adverse event with no serious or unexpected adverse events.

CONCLUSION: SV-BR-1-GM in this regimen appears to be safe and well-tolerated and is associated with objective regression of metastatic breast cancer. HLA matching is being studied as a predictor of response.

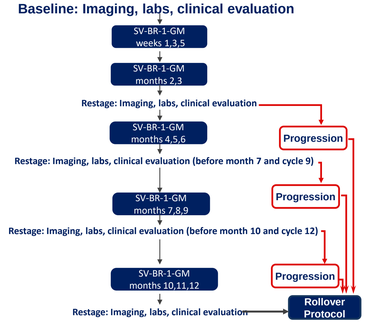
Table of Patients

Patient	Age	Metastatic Sites	# Prior Regimens	HLA Matches	# of Cycles	Tumor Regression?
01-001	46	Pleura Lymph Nodes	7 chemo/bio 5 hormonal	DRB3*02:02	1	No
01-002	73	Lung Liver Bone	7 chemo 1 hormonal	A*24:02 DRB3*02:02	8	Lungs
01-005	54	Lymph nodes Pleura Skin	3 chemo/bio	A*24:02	2	Skin
02-001	70	Lymph nodes	3 chemo/bio	None	1	No
02-003	61	Bone Brain	3 chemo	None	6	Pending
02-004	74	Lymph nodes Cutaneous	5 chemo	(A*11:01) DRB3*02:02	2	Pending

PERSPECTIVE

- SV-BR-1-GM is a whole-cell targeted immunotherapy prepared from a breast cancer cell line with an unusual variety of cytogenetic abnormalities (Wiseman and Kharazi, 2006 and 2010).
- In a small initial clinical trial, one "Special Responder" experienced prompt, widespread, and replicable regression at multiple sites of metastatic breast cancer (Wiseman and Kharazi, 2006). This patient appeared to match SV-BR-1-GM at key HLA loci.
- Histocompatibility allele match(es) between SV-BR-1-GM and patients may improve therapeutic efficacy assuming a mechanism of action in which patient T cells are activated via cancer antigens co-expressed in SV-BR-1-GM and patient tumors and displayed on SV-BR-1-GM HLA molecules.
- This Phase I/IIa study evaluates the safety and preliminary efficacy of SV-BR-1-GM in patients with advanced breast cancer

Study Flow



METHODS

Clinical Protocol WRI-GEV-007 (ClinicalTrials.gov NCT03066947)

- SV-BR-1-GM is a breast cancer cell line with features of immune cells (See Lacher et al. Poster 5632), The cell line is grown in simple tissue culture media under GMP conditions (University of California, Davis, GMP facility). Prior to inoculation, the cells are serum starved for 24 hours and then irradiated (20,000 cGy) prior to inoculation. The cells are shipped at 4 ºC to the site and injected intradermally within 24 hours. The regimen includes
  - Pre-dose cyclophosphamide (300 mg/m²) 2-3 days prior to SV-BR-1-GM inoculation;
  - 20 million irradiated SV-BR-1-GM cells inoculated intradermally split into 4 inoculations (x2 in the thighs and x2 in the upper back);
  - Interferon-α2b intradermally (10,000 IU per inoculation site) ~2 and ~4 days following SV-BR-1-GM inoculation.
- Treatment is performed every 2 weeks for the first month and then every month with evaluation every 8-12 weeks.
- Inclusion criteria include histological confirmation of breast cancer with recurrent and/or metastatic lesions with evidence of persistent, recurrent, or progressive disease for which there is no known or established treatment available with curative intent, after failing at least one course of community standard systemic treatment with chemotherapy (and endocrine therapy if appropriate)

Key exclusion criteria include concurrent or recent chemotherapy (3 weeks), XRT (1 week), or general anesthesia/major surgery (3 weeks), and a treatment-free "washout" period of 3 weeks before starting this program (8 weeks for persons receiving nitrosourea or mitomycin).

Objectives

Primary Objective: To evaluate the number, frequency, duration, and relation of toxicity events to SV-BR-1-GM, as defined by CTCAE and additional tests.

Secondary Objectives: To evaluate tumor response:

1. Objective response rate (ORR), defined as complete response (CR) or partial response (PR) per RECIST and iRECIST response criteria
2. Non-progressive rate, defined as CR, PR or stable disease (SD) per RECIST and iRECIST
3. Durability of response.

Exploratory Objectives:

1. To assess immune responses to SV-BR-1-GM, and to recall antigens, if any, as measured by DTH skin tests and/or other immunological tests.
2. To gather pharmacodynamic data including histocompatibility characterization, levels of circulating cytokines, antibodies and cell mediated immune responses.
3. To measure the quality of life (QOL), changes in weight, performance status, and pain.

RESULTS

Patient Characteristics

Patient	Histologic Dx	Duration of Disease	Metastatic Sites	Prior Treatments
01-001	Poorly Differentiated ER&PR+ HER2/neu (+) Ki-67 = 25%	7 years	Pleura Lymph Nodes	1. Neoadjuvant doxorubicin, Cytoxan & docetaxel 2. Doxorubicin liposomal injection & Cytoxan 3. Capecitabine 4. Pertuzumab, trastuzumab & paclitaxel 5. Ado-trastuzumab emtansine 6. Lapatinib & capecitabine 7. Eribulin Adjuvant Radiation 1. Tamoxifen 2. Triptorelin 3. Letrozole 4. Fulvestrant 5. Aromasin
01-002	Well-differentiated DCIS ductal ER/PR (+) HER2/neu (-) Ki-67 unknown	12 years	Liver Lung	1. Doxorubicin, Cytoxan & docetaxel 2. Exemestane 3. Docetaxel & Cytoxan 4. Gemcitabine 5. Abraxane 6. Palbociclib & exemestane 7. Capecitabine Prior radiation of mets 1. Anastrozole
01-005	Poorly differentiated Ductal ER & PR negative HER2/neu 3+ Ki-67 unknown	3 years	Lymph nodes Pleura Cutaneous	1. Neoadjuvant docetaxel, carboplatin, trastuzumab & pertuzumab 2. Neo-adjuvant Trastuzumab 3. Neo-adjuvant pertuzumab, trastuzumab & capecitabine
02-001	Poorly differentiated Ductal ER & PR negative HER2/neu 1+/neg Ki-67 = 90%	2 years	Lymph nodes	1. Cyclophosphamide & Doxorubicin 2. Taxol 3. Trastuzumab
02-003	Poorly differentiated Ductal ER & PR unknown HER2/neu 1+ Ki-67 68%	6 years	Bone	1. Neo-adjuvant carboplatin & paclitaxel 2. Adjuvant doxorubicin & cyclophosphamide 3. Adjuvant carboplatin & paclitaxel Adjuvant and metastatic radiation
02-004	Poorly differentiated Ductal ER & PR + HER2/neu neg Ki-67 90%	3 years	Lymph nodes Cutaneous	1. Adjuvant Docetaxel & Cyclophosphamide 2. Vinorelbine, Trastuzumab & pertuzumab 3. Faslodex & Ibrance 4. Doxorubicin & Carboplatin 5. Ixabepilone

Serious Adverse Events

Subject	Body System	AE Term	Severity	Relationship
01-001	Respiratory	Respiratory Failure	Grade 4	Unrelated
01-005	Cardiac	Restrictive Cardiomyopathy	Grade 4	Unlikely Related

Related Adverse Events

All Related Adverse Events-by Body System

Body System AE	AE Term	Grade 1 n=27 (96%)	Grade 2 n=0 (0%)	Grade 3 n=3 (4%)	Total n=30 (100%)
General Disorders and Administration Site Conditions		13	0	1	14
	Erythema	12			
	Fatigue	1			
	Dehydration			1	
Skin and Subcutaneous Tissue Disorders		13	0	1	14
	Induration	10			
	Pruritis	3			
	Breast Pain			1	
Gastrointestinal Disorders		1	0	1	2
	Diarrhea	1			
	Vomiting			1	

Patient Treatment, Response and HLA Type

	# of Cycles	Tumor regression	HLA-A Alleles		HLA-B Alleles		HLA-DRB3/4/5 Alleles	
SV-BR-1-GM			11:01*	24:02	35:08	55:01	3*01:01	3*02:02
Patient 01-001	1	No	02:01	03:01	15:01	40:02		3*02:02
Patient 01-002	8	In Lung	03:01	24:02	15:01	51:01		3*02:02
Patient 01-005	2	In Skin	24:02	33:01	07:02	49:01	4*01:01	
Patient 02-001	1	No	02:01	03:01	35:01	51:01	4*01:01	5*01:01
Patient 02-003	6	No	01:01	02:05	49:01	53:01	3*03:01	4*01:01
Patient 02-004	2	Lost to F/U	03:01	11:01*	07:02	55:02	3*02:02	5*01:01

*Note that initial testing suggests that HLA-A*11:01 is not expressed in SV-BR-1-GM

Patient Notes:

Patient 01-001: 46 year-old, dropped out after first dose due to respiratory failure, then was treated off protocol for several cycles prior to going on hospice. Did appear to derive some clinical benefit.

Patient 01-002: 73-year-old with lung and liver metastases. After 6 cycles (3 months on treatment) clear response in the lung lesions (see images, table), liver lesions stable to slightly enlarged. Liver lesions progressed after 6 months, lung lesions remained stable (see table).

Patient 01-005: 54-year-old was responding clinically in cutaneous breast lesions. After 2nd dose, pleural and pericardial effusions worsened, developed fatal restrictive cardiomyopathy, judged unlikey related.

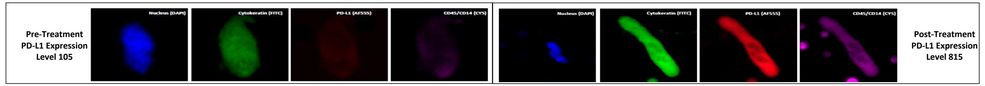
Patient 02-001: 70-year-old received one cycle and then dropped out and entered hospice.

Patient 02-003: 61-year-old has received 6 cycles, no clinical response, then went off study.

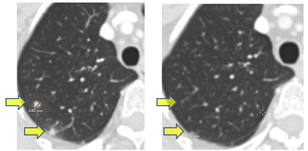
Patient 02-004: 74-year-old with inflammatory breast cancer, received 2 cycles and then withdrew, AE of "open wounds/pain from breast cancer", probably related to treatment. Lost to follow-up, no other imaging done.

Patient 01-002 Circulating Tumor Cell Analyses

Circulating Tumor Cells and Circulating Cancer-Associated Macrophage-Like Cells were analyzed for PD-L1 Expression. Mean levels increased from 97 ±7 to 437 ±72 (SEM). Representative Photos are Shown Below

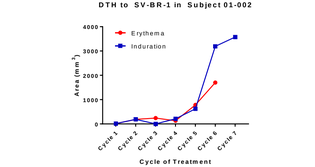


Patient 01-002 Imaging & DTH



Pt. 01-002: 73 y.o. female breast cancer patient, progressive lesions lung, liver, bone despite 7 previous chemo regimens. Baseline and 3 mo. (5 cycles) images of 2 of 20 regressing lung metastases (arrows). Images at 6 months (not shown) similar- no relapse, no new lesions. Note virtual complete regressions of lung metastases, other 18 metastases regressed similar to above, see Table on right.

	Pt 01-002 CT Scan Lung Images		
Site	Size (mm) pre-Rx	Size mm- 3 months	Size mm- 6 months
RLL	2.9	Not Detectable	Not Detectable
LUL	3.4	tiny nodule < 1mm ?scar	tiny nodule < 1mm ?scar
XXX	3.9	Not Detectable	Not Detectable
XXX	4.0	Not Detectable	Not Detectable
RLL	4.5	Not Detectable	Not Detectable
LLL	4.9	Not Detectable	Not Detectable
XXX	5.2	Not Detectable	Not Detectable
RLL	5.2	Not Detectable	Not Detectable
RLL	5.6	Not Detectable	Not Detectable
RLL	5.6	Not Detectable	Not Detectable
XXX	5.8	Not Detectable	Not Detectable
LUL	6.0	Not Detectable	Not Detectable
XXX	6.7	1.5	1.5
RUL	7.2	1.5	1.5
LLL	7.6	Not Detectable	Not Detectable
RUL	7.7	Not Detectable	Not Detectable
RLL	7.9	1.0	1.0
RUL	8.2	Not Detectable	Not Detectable
RLL	9.0	Not Detectable	Not Detectable
RLL	9.1	< 0.1	< 0.1



All patients had immediate and delayed type hypersensitivity measured to the irradiated SV-BR-1 parent cell line (1 million cells injected intradermally into the forearm). Patient 01-002 was the only patient with multiple evaluations who developed a robust DTH response to SV-BR-1

DISCUSSION

SUMMARY

- **SV-BR-1-GM has been administered to 6 patients in this Phase I/IIa study**
- **Treatment has generally been safe and well tolerated**
  The most frequent adverse events were injection-site related erythema, induration and pruritis
- **Two patients had documented clinical regressions, one in multiple metastatic lung lesions and one in cutaneous metastases**
- **Matching of the patients HLA type with SV-BR-1-GM was seen in both of these patients (one at Class I HLA and Class II HLA loci and one at Class I only)**
- **The patient with regression of lung metastases also exhibited a robust DTH response to the parent cell line (SV-BR-1)**
- **This patient demonstrated apparent upregulation of PD-L1 expression on circulating cancer-associated macrophage-like cells, potentially associated with progression in the liver**

CONCLUSIONS

While confirmatory studies will be required, the data implies the following:

1. SV-BR-1-GM in the regimen evaluated here appears to be safe and well-tolerated
2. SV-BR-1-GM in the regimen evaluated here can produce clinically relevant regression of widespread metastases in patients with metastatic breast cancer
3. Response to the SV-BR-1-GM regimen appears to be more likely in patients who match with SV-BR-1-GM at one or more HLA loci
4. In one patient who responded with regression of lung lesions, apparent upregulation of PD-L1 was seen in circulating cancer-associated macrophage-like cells
5. Further study of the SV-BR-1-GM regimen, as well as combination therapy with immune checkpoint inhibitors, appears warranted.
   - A roll-over study for patients who develop progressive disease is available where they can be treated in combination with pembrolizumab or ipilimumab (depending on the PD-L1/2 status of their tumors) (listed in ClinicalTrials.gov as NCT03328026)

REFERENCES

- Lacher ML, et al, Frontiers in Immunology (in press)
- Wiseman and Kharazi, Breast J. 2006;12(5):475-80.
- Wiseman and Kharazi, The Open Breast Cancer Journal 02/2010; 2(1):4-11.

ACKNOWLEDGEMENTS

We are grateful to Gerhard Bauer, Brian Fury, Emily Lynn Fledderman, Tye Daniel Petrie, Dane P. Coleal-Bergum, and Tia M. Hackett from the UC Davis GMP facility (Sacramento, CA) for their SV-BR-1-GM manufacturing efforts.
We thank Mepur Ravindranath and his team at Terasaki Laboratories for providing their HLA typing services.
We thank Peter Amstutz, Cha-Mei Tang and the team at Creatv Microtech for their circulating tumor cell analyses.