TITLE PAGE:

Study Title:	A Phase I/IIa Study of SV-BR-1-GM in Metastatic or Locally Recurrent Breast Cancer Patients
Study Sponsor:	BriaCell Therapeutics Corp 820 Heinz Ave. Berkeley, CA 94710 Tel: 888-485-6340 FAX: 424-245-3719
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Study ID Number:	WRI-GEV-007
Intended use:	Treatment of Stage IV Breast Cancer with special consideration to CNS metastases

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CONFIDENTIALITY STATEMENT

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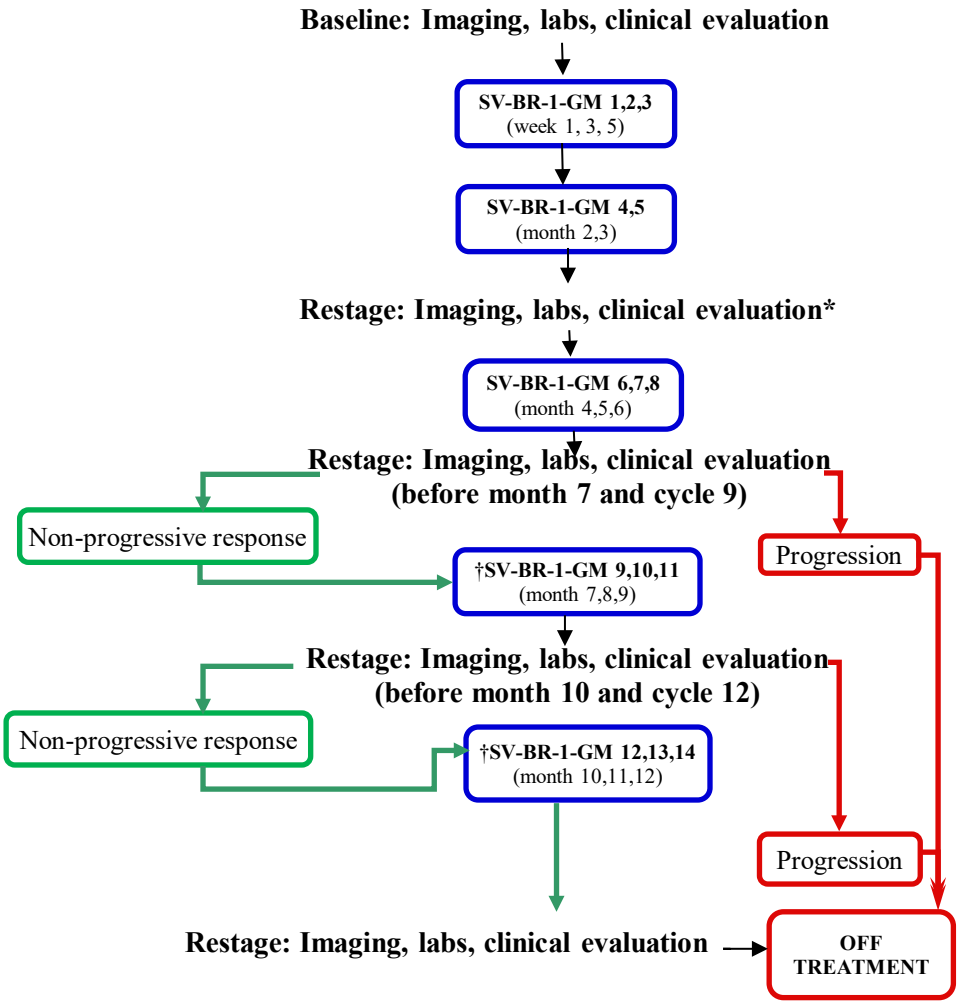


* Restaging to occur between Treatment 4 and 6. Patients with rapid progression may go off-study per PI.

†Continuation to Treatment 8 is mandatory unless rapidly progressive in opinion of PI; Treatments 9-14 are optional and the patients must fullfill the criteria of non-progressive disease and desire to continue treatments.

NOTE: Grade III hypersensitivity or IV toxicity at ANY step will warrant special review; see Toxicity

Flexibility between cycles can be +/- within one week under special circumstances as approved by PI.

1. INTRODUCTION

This Phase I/IIa study is designed to evaluate the safety and efficacy of, using SV-BR-1-GM, a breast cancer cll line genetically engineered to secrete GM-CSF and consequently augments dendritic cell activity [1-4]. A breast cancer cell line is expected to contain one or more putative tumor rejection antigens; for non-breast cancer cases, eligibility requires the subject's tumor also to have evidence of HER2/neu positivity, which is commonly reported as 20-30% of cases in the published literature [5].

Previous work with this program demonstrated prompt and near-complete regression of multiple sites of metastatic breast cancer involving brain, and therefore special consideration is given to allow protocol entry to selected patients with central nervous system (CNS) involvement.

Each experimental administration cycle comprises of 4 intra-dermal injections. This will be given 3 times as a cycle: once every 2 weeks during the initial phase.

Each cycle will be comprised of 4 study events (and location)
1. Pre-SV-BR-1-GM cyclophosphamide (physician's office)
2. SV-BR-1-GM inoculation (physician's office)
3. Interferon-alpha-2b (Merck) at 2 days post- SV-BR-1-GM (physician's office)
4. Interferon-alpha-2b (Merck) at 4 days post- SV-BR-1-GM (physician's office)

A Quality of Life questionnaire (SF-36) will be administered at the start of each cycle. The evaluation of safety and clinical developments will be assessed at every study visit after starting the SV-BR-1-GM therapy cycles. The first three cycles will occur over one month at Weeks 1, 3, and 5. This will be followed by monthly cycles for a total of 6 months; with optional treatments out to a year. Imaging and restaging will occur between the 4^{th} and 6^{th} inoculations (e.g. about month 2-3). In the absence of progressive disease (defined below) or major safety issues, the patient will continue with additional SV-BR-1-GM therapy cycles to complete 6 months of experimental SV-BR-1-GM administration, with restaging every 3 months at approximately 3 weeks following the last treatment. If the patient remains non-progressive and desires to continue treatment after six months they will be offered an additional three months of treatment followed with restaging at nine months. Again, if the patient has non-progressive disease and desires to continue treatment, they will be offered an additional 3 months of treatment, with completion at 12 months.

Table 1: SV-BR-1-GM CYCLES

Week #	Cycle	Comments
1, 3, 5	1, 2, 3	
Month #		
2, 3	4, 5	Restaging about 1-2 weeks prior to initiation of next cycle (#6)
4, 5, 6,	6, 7, 8	Restaging about 1-2 weeks prior to initiation of next cycle (#9)
Optional Treatment Cycles		Patient may continue if they show non-progressive response
7, 8, 9	9, 10, 11	Restaging about 1-2 weeks prior to initiation of next cycle (#12)
Optional Treatment Cycles		Patient may continue if they show non-progressive response
10, 11, 12	12, 13, 14	Off-treatment evaluation about 6-8 weeks after last inoculation cycle

Flexibility between cycles can be +/- within one week under special circumstances as approved by PI.

The schedule is also provided graphically in Figure 1, "Program Schema."

To boost the immune response, patients will be pretreated with low-dose cyclophosphamide that has been shown to down-regulate T regulatory-cell mechanisms [6-9] 2-3 days prior to each SV-BR-1-GM inoculation. Low-dose Interferon-alpha-2b (Merck) serves as an adjuvant [10,11] and is given by intradermal injection to the inoculation site 2 days and 4 days after SV-BR-1-GM inoculation. Biological specimens will be collected at regular intervals per protocol, and stored in a repository (with subject permission) pending future research by the sponsor. Collection, labeling, and storage of these specimens will follow the procedures outlined in a separate Laboratory Manual. Study procedures involving subjects (e.g. screening, inoculation, follow-up visits, etc.) will take place at trial sites. SV-BR-1-GM manufacturing, quality control, preparation, and study laboratory tests will take place at the sponsor's research facility. SV-BR-1-GM and specimens will be transported to the sites using appropriate procedures summarized in Section 9.4.5.

Study participants will be closely monitored for adverse events (toxicity) using the common terminology criteria for adverse events (CTCAE v 4.03) scale. Development of Grade IV toxicity in any subject will truncate accrual until further review by the medical monitor, IRB and FDA as appropriate. Development of a new or progressive tumor, or treatment-related Grade III allergy/hypersensitivity, will truncate further inoculations to any particular subject. We have previously reported results on 4 patients included remarkable responses and positive improvement of survival [12]. Given the initial development of even minimal evidence of host responses, and absence of toxicity, we plan to test 10 patients and plan to perform a safety analysis. Once deemed safe, an additional cohort of 15-30 patients (up to total of 25-40) will be enrolled. Patients who do not reach the initial post-dose tumor assessments may be replaced at the discretion of the Sponsor.

Each patient will be on treatment for 6-12 months and no extended follow up. Any future research on specimens collected during this study will be controlled by a separate, IRB-approved protocol; to be developed as the need arises.

1.1. BACKGROUND

1.1.1. General Background of the Experimental Product

SV-BR-1-GM is an experimental, HER-2/neu positive, allogeneic, whole cell breast tumor cell line transfected with the GM-CSF gene to secrete GM-CSF *in situ* and consequently augment dendritic cell activity [15-18]. This biological product has been previously granted an IND by the FDA for investigational use only under BB-IND-10312, under the designation SV-BR-1-GM. Documentation of initial tumor regression has been published [19]. This preliminary data is especially notable for demonstrating regression of brain metastases and for the reinduction of response with retreatment. Regression of brain metastases has not been commonly reported in such studies. However, we observed regression in a patient on this protocol. To note, such regression was also seen in another patient, previously treated by our group under another protocol, BB-IND-2749 [20].

1.1.2. Background of the Target Condition - Cancer

Cancer of all types is one of the biggest medical public health problems in the world. This study can provide a template for looking at the effects of the investigational product known as SV-BR-1-GM on various types of cancer. For the current protocol, we emphasize that HER2/neu antigens on SV-BR-1-GM are strongly over-expressed and that similar over-expression is a feature not unique to breast cancer. Approximately 20-30% of prostate, lung, ovary, gastric, pancreatic, colon, bladder, and other categories of human malignancy may display HER2/neu antigenic over-expression, albeit not necessarily having similar molecular biology or prognostic features as breast cancer. The possibility certainly exists that SV-BR-1-GM with over-expression of known and defined antigen, might have applications for other tumor types.

But to consider only breast cancer, we address a public health problem of enormous magnitude. Worldwide, an estimated 500,000 women will die from this disease each year. In the US, 1 in 8 women will contract the disease, and, despite some progress in therapy, the majority of patients with metastatic breast cancer will ultimately die within 3 years [21] (See also http://www.cancer.gov/cancerinfo).

While complete responses are certainly not uncommon in general clinical practice, an analysis by Greenberg, et al. of 1581 patients at the M.D. Anderson Hospital and Tumor Institute demonstrated this outcome occurred in only 16.6%, and by 5 years, only 3.1% were still in complete remission [22]. The natural history of metastatic breast cancer in 2003 can still be appropriately compared to studies 25 years ago [23]. Fossati's review of published randomized trials, involving 31,510 metastatic breast cancer patients [21] did indicate progress, but certainly new and more effective therapies are needed. There is a possibility that targeted immunotherapies (also known as therapeutic cancer vaccines) will be useful, and the Physicians Data Query (PDQ) compilation describes such clinical trials in progress throughout the United States.

1.1.2.1. Clinical Immunology and Immunotherapy

The efforts of many researchers have suggested the presence of breast cancer-associated antigens, including CEA, T/Tn, MAGE, MUC-1, and others [24]. A comprehensive review is beyond the scope of this protocol. Previously, Renkvist et al. [25] made a catalog of tumor-associated antigens recognized by T-cells, of which breast-cancer related antigens are frequently noted. A more recent compilation has been published in the open journal Cancer Immunity by van der Bruggen [26].

Previously, the establishment of a large library of breast cancer cell lines, together with available autologous serum, supported the sponsor's earlier studies of tumor-specific host immune responses [27]. These cell lines included the often studied MDA-MB-231, -435, -156, and others. Indirect immunofluorescent antibody assays detected autologous reactivity to established breast cancer cell lines in 8 of 10 patients; reactivity remained present after absorption with heterophile antigens, normal breast tissue, and AB+ human red cells. These reactions occurred in 40-66% of allogeneic sera samples from breast cancer patients, and were not explainable as reactions to CEA. Additional work indicated both humoral and cell-mediated reactivity [28, 29] to antigens related to mouse mammary tumor virus. There has been renewed interest [30] in the possibility that human breast cancer may involve an agent similar to mouse mammary tumor virus. Those early serological studies as well as *in vitro* studies of cell-mediated immunity were consistent with this still-unresolved hypothesis.

Breast cancer may have antigens related to the Thompson-Friedenreich blood group antigen [31]. The sponsor has had an interest in these antigens, and performed a small survey of cellular and humoral responses to a commercial "T-antigen" preparation (Wiseman et al, unpublished). To note, others have pursued this area, even to the point of very large Phase III clinical trials [32]. Given the existence of known and putative breast-cancer associated antigens, there are many options for creating cancer targeted immunotherapies [7]. Questions persist regarding the use of whole-cell vs. tumor lysates, autologous antigens vs. chemically defined antigens, and other treatment variables Issues on dose, route, schedule and duration of therapy require much further investigation, especially in the absence of a commonly-accepted surrogate marker of immune response [33, 34]. Even if available, the evaluation of disease-free and overall survival is the ultimate, practical outcome measure, in conjunction with toxicity and impairment (or lack thereof) of one's quality of life.

Targeted immunotherapy has been associated with regression of bulky, macroscopic tumors. Our group described such results, notably, in a melanoma patient, involving a change in tumor volume on the order of 800 cc [35]. Others have also reported tumor regressions in advanced cancer, and in particular, breast cancer. Jiang et al. reported using subcutaneous injections of autologous and allogeneic MCF-7 breast cancer cells, together with CA15-3, CEA, CA125 plus IL-2 and GM-CSF in 42 patients with advanced breast cancer, and observed clinical regression in 2 patients, one of whom had complete disappearance of hepatic metastases [36]. Krause et al. have been applying a dendritic cell immunotherapy program to breast cancer as well as melanoma [37] and have observed several breast cancer patients with major regression of advanced, metastatic tumor, one of whom had a response of such intensity as to precipitate tumor lysis syndrome [38]. The early reports on sialyl-Tn immunotherapy identified partial responses in 3 of 12 patients [39] although, as mentioned, a Phase III clinical trial by the Biomira Corp.

failed to achieve the predetermined statistical endpoints of improvement in time to disease progression and overall survival.

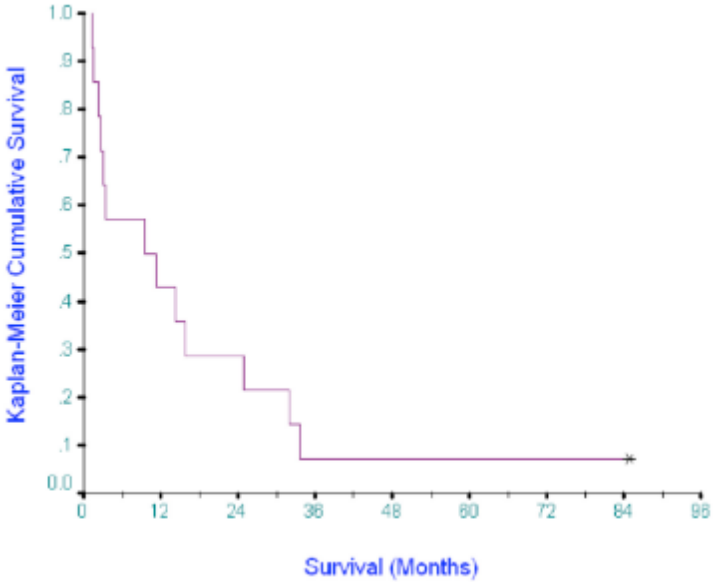
Disis et al. have demonstrated that frequent and durable immune responses to HER2/neu can be generated [40]. This study also employed GM-CSF in conjunction with peptides of the HER2/neu receptor antigen. Of 64 patients with over-expression of HER2/neu (including ovarian and non-small cell lung cancer), 92% demonstrated immune responses to the immunizing antigen, and persistence of same for at least 12 months. Moreover, the phenomenon of epitope-spreading was documented as well. The overall implications for clinical outcome remain inconclusive, however.
Whole cell preparations continue to hold appeal for targeted cancer immunotherapy studies, especially given the report of 3 of 33 complete remissions in lung cancer with a whole-cell preparation transfected with GM-CSF [41]. We note that the plasmid-transfection methodology used here has the potential to provide a more stable and more sustained level of GM-CSF production than other transfection techniques. Given our current lack of knowledge of the presence and distribution of the relevant tumor-associated antigen(s) [42], whole cells may have the advantage of providing a large repertoire of both membrane and cytoplasmic antigens, and, while some antigens have been characterized, it is likely many more remain to be identified.

1.1.2.2. Work done by Dr. Charles Wiseman & Colleagues

The research program of the sponsor, Dr. Wiseman, has used whole-cell targeted immunotherapies in a variety of human malignancies, including melanoma and pancreatic cancer. More recently, he has evaluated a cohort of breast cancer patients treated with a cell line established in his laboratory and administered in conjunction with GM-CSF. This particular cell line, designated SV-BR-1 is fast growing and has strong expression of the HER2/neu antigen, an immunogenic neoantigen that has been shown to be overexpressed by a high number of breast tumors [43].

Data have been presented describing a small cohort of patients with very advanced stage IV breast cancer inoculated with a targeted immonotherapy consisting of 10-20 $x10^6$ irradiated tumor cells (SV-BR-1). SV-BR-1 was administered by lymphangiogram technique, intralymphatic technique or intradermally admixed with an equal number of cryopreserved peripheral blood lymphocytes obtained by leukapheresis [44]. Patients were pretreated with low-dose cyclophosphamide 300mg/m^2 2-3 days prior to SV-BR-1 and received subcutaneous injections of GM-CSF just prior, and for 8 days after, SV-BR-1 inoculation. Toxicity included one patient with increasing ascites and abdominal discomfort during the GM-CSF injections and another patient who developed, following cyclophosphamide, exacerbation of pericardial effusion and atrial fibrillation, which spontaneously resolved. It is unclear if these are really adverse effects from the inoculations or natural progression of un-responding breast cancer. There were 4 patients surviving more than 12 months. One patient is alive at 156 months. (See Figure 2 below)

Figure 2: SURVIVAL OF 14 BREAST CANCER PATIENTS TREATED WITH PBL/ID TUMOR CELL PREPARATION (SV-BR-1)



1.1.3. Alternative Treatments for Cancer

1.1.3.1. Strategies for tumor therapy

An effective therapy for patients with advanced malignancy would produce tumor regression to detectable levels, would extend the time to relapse, and would improve survival. Should malignant transformation occur again by whatever mechanism previously involved with the initial tumor, host defenses would prevent *de novo* tumor growth.

Current thinking about cancer biology asserts that cancer is a clonal population that rapidly becomes heterogeneous. Tumor growth follows Gompertzian kinetics and chemotherapy works via first order kinetics [45]. Since clinical tumors have been present but undetectable for 90% or more of the lifespan of the malignancy, whatever host immune response they might have elicited must have been somehow nullified. Immunotherapy to be effective must reverse this state of tolerance [46, 47]. Current understanding of the key mechanism of immune cytotoxicity favors a process mediated by CD8+ T-lymphocytes, although important contributions by NK-cells, antibody, and other mechanisms are not discounted [48,49].
While these and other theoretical concepts above are receiving intense reappraisal, the necessary and sufficient conditions for effective therapy are not known, and intermediate processes will be much better understood if and when reliable surrogate markers of effective immunization have been identified [50]. A promising new test, the Cell Search assay, which quantifies circulating breast cancer cells, may be useful for the identification of early response (or lack thereof) [51] long before there is indication of tumor regression by the usual imaging techniques.
The kinetics of immune response may also play a very important role. The sponsor of this study has collaborated with a number of mathematicians (Mathematics of Medical Oncology Study Group), resulting in a publication [52]. The sponsor also helped organize an international meeting sponsored by the American Institute of Mathematics (www.aimath.org) (The Modeling

of Cancer Progression and Immunotherapy December 12 to December 16, 2005 at the American Institute of Mathematics, Palo Alto, California organized by Lisette de Pillis, Ami Radunskaya, and Charles Wiseman). From various studies in the public domain, the publication mentioned above describes a computer simulation based on the following differential equations:

$$\frac{dT}{dt} = aT(1 - bT) - cNT - D \qquad \text{(A)}$$

$$\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h + T^2}N - pNT \qquad \text{(B)}$$

$$\frac{dL}{dt} = -mL + \frac{jD^2}{k + D^2}L - qLT + rNT \qquad \text{(C)}$$

where

$$D = d\frac{(L/T)^\lambda}{s + (L/T)^\lambda}T \qquad \text{(D)}$$

$T(t)$, tumor cell population at time t;
$N(t)$, total level of NK cell effectiveness at time t;
and $L(t)$, total level of tumor-specific $CD8^+$ T-cell effectiveness at time t.

The model documented the importance of both NK cell and CD8+ cytotoxicity, a difference in the dynamics of their response, and the utility of currently available immuno-monitoring methods. Sensitivity analysis emphasized a primary role of patient-specific responses. Refinements to this model are ongoing, but this study provides an obvious resource for generating data useful for hypothesis testing of the computer model. This model was based on kinetics of a mouse tumor, but was in part validated using published data from clinical immunotherapy investigations in humans. Clearly strategies do exist with the potential to help develop clonal proliferation of tumor-specific effector cells from antigen primed memory T-cells [53]. Remarkably, increasing number of reports are appearing which demonstrate up-regulation of cytotoxic T-lymphocytes after targeted immunotherapy; a change that occurs despite the abundance of antigen that must already be circulating in patients with tumor.
The immune response begins with antigen presentation, which is believed to be mediated mostly by dendritic cells, the most active of the "professional" antigen-presenting cells. Dendritic cell differentiation can be augmented by GM-CSF, a lymphokine currently used for protecting marrow during intense chemotherapy [54]. The application of GM-CSF in clinical trials has extended from the evaluation of effects as a single agent [55], to combining with targeted tumor immunotherapies [56,57] and to use in creating genetically-engineered tumor cell immunotherapies that release GM-CSF locally [58,59]. In addition, many of these studies of GM-CSF modulated immunotherapy are now including the use of currently-available chemotherapy [60, 61].

1.1.4. Previous Studies

The sponsor, Dr.Wiseman, was involved with the Immunotherapy Laboratory at St. Vincent Medical Center, Los Angeles, up until 2006. During that time, he had been involved with

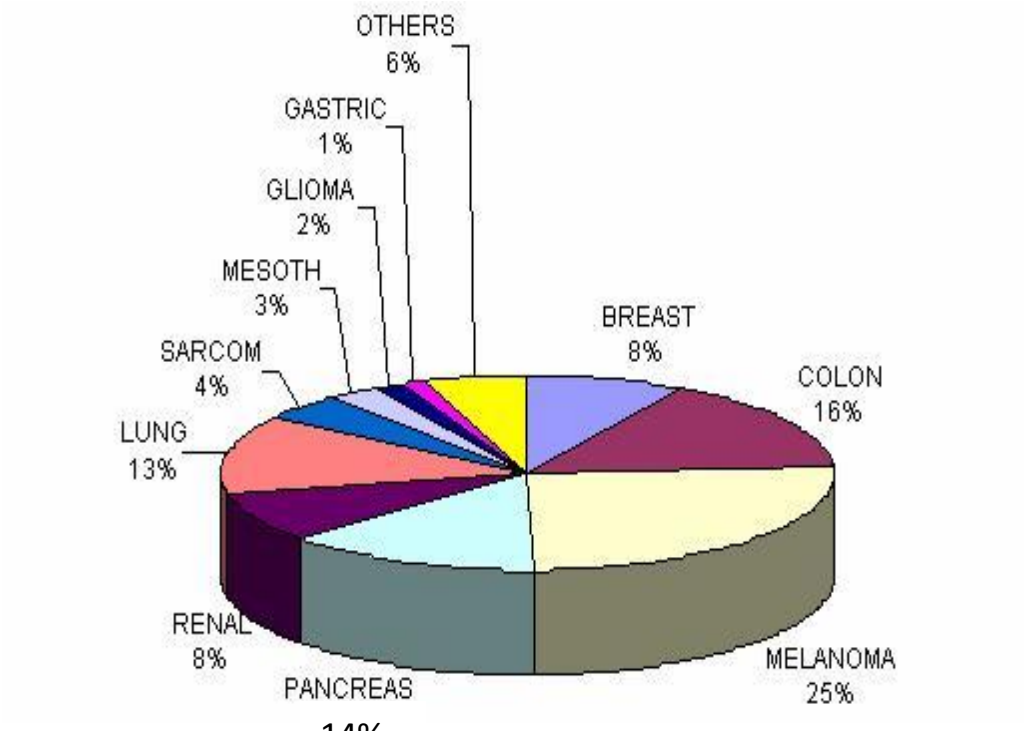
establishing a program of investigations of whole-cell tumor preparation through IND BB-2749. Initially concerned with preparing single-cell suspensions of tumor cells for application in the autologous setting, this research program had evolved to provide off-the-shelf whole tumor cell preparations in the event autologous tumor was not available. Over the years there has been a series of different modifications to the original clinical trial program of autologous or allogeneic whole cell targeted immunotherapies. Some of the principal changes are shown below:

EVOLUTION OF TARGETED IMMUNOTHERAPY STUDIES

1. Fresh frozen tumor cells
2. Pre-treatment of patients enrolled with low-dose Cyclophosphamide
3. Cholesteryl Hemisuccinate for Antigen Up-regulation
4. Cy+ CHS/Targeted Immunotherapy +IL-2
5. IFN-alpha treatment of tumor cells for Antigen Up-regulation
6. GM-CSF administration
7. IFN-gamma treatment of tumor cells for Antigen Up-regulation
8. Tumor cell/PBL Co-inoculum
9. Genetically-engineered whole tumor cell preparations

More than 250 patients have been studied under this program (BB-IND 2749) in its various iterations and modifications. While melanoma was initially our major concern, changes in referral pattern have encouraged study of other tumor types as well. (See Figure 3 below):

Figure 3: Types of Cancer Studied Under BB-IND 2749



The initial strategy of our program was to evaluate small cohorts in sequential Phase 1 studies:

DESIGN OF CLINICAL TRIALS

1. Evaluate cohort:
   a. If >1 of 14 objective responses, continue accrual
   b. If Grade IV toxicity, suspend study, consult FDA; redesign as needed
   c. If >30% response, plan for publication and further clinical trial studies
   d. If 10-20%, evaluate possible prognostic factors, review literature, redesign the clinical trial

2. Ongoing collection to bank serum, plasma, lymphocytes, tumor tissues (available basis), etc. for further correlative study

3. Critical review of clinical and possible surrogate endpoints

More recently, the sponsor has been involved with evaluating the role of subcutaneous GM-CSF administered simultaneously with targeted immunotherapies under this previously approved IND, BB- IND-10312. Data has been reported at major meetings for his work with breast cancer [62], melanoma [63] pancreatic cancer [64, 65], renal carcinoma [66], and lung cancer [67]. A presentation at the Society of Biological Therapy in October 2006 [68] described TWO patients with regression of brain metastases during targeted immunotherapy: one patient described in the publication above; another treated under a different protocol (BB-IND 2749). Dr. Wiseman is now assuming the role of sponsor -BriaCell Therapeutics- under Part 312 of the Federal regulations, and thus, the research in this protocol will be performed by outside principal investigators.

1.1.5. Evaluation of Previous Studies

The possibility of 'subclinical regressions' deserves further study as the reliance on imaging methods may be insensitive. Leung et al. described a program of neoadjuvant therapy for hepatoma, which did not appear to have any efficacy according to CAT scan and radiologic imaging [69]. However, some cases proceeded to surgical resection and showed only fibrosis and scarring; this complete pathological response would not have been recognized at all by the usual radiological techniques. A similar finding was reported for pancreatic cancer, with 2 of 15 patients in complete pathological remission identifiable only after surgical resection [70]. Clinical use of serum markers may provide an opportunity to identify such 'subclinical responses', at least for some malignancies. Our work with pancreatic cancer fits this paradigm of possible increased survival associated with targeted immunotherapy in the absence of identifiable changes in measurable or evaluable metastatic lesions.

Wiseman and colleagues [71] treated 17 evaluable pancreatic cancer patients with allogeneic targeted immunotherapy prepared from culture of the cell line MiaPaca (ATCC). For 7 of the 17 patients having a drop in CA 19-9 equal to or greater than 20%, the survival was 8.3 months; for those not showing such biological effect, the median survival was 4.0 months. Survival *versus* change in CA 19-9 had correlation-with a statistically significant value: p =0.007 [71].

1.1.6. Plans for This Study

This study will address safety, feasibility and toxicity, and plan for the investigation of clinical (or immunological) responses. As mentioned above, we have published results of a study finding widespread clinical regressions in breast cancer. Results from the current study will possibly support or preclude expansion to Phase II and Phase III studies under this IND.

At the initiation of dosing in this study, the Food and Drug Administration (FDA) requested that the first three patients be dosed sequentially, with at least 2 weeks between patients, to evaluate the safety of SV-BR-1-GM. This phase of the study was completed as of 27 September 2017 and no safety issues related to SV-BR-1-GM were noted that would limit continued dosing in these patients or preclude dosing additional patients. With this phase of the study completed, the second phase of the study commenced where patients can be enrolled and dosed simultaneously. This marks the transition from the Phase I to the Phase IIa part of the study.

In addition, one patient developed a fatal serious adverse event on study. The patient was a 54-year-old woman with metastatic breast cancer involving one breast, including cutaneous metastases, and the pleura with a large pleural effusion. Prior treatment had included neo-adjuvant docetaxel, carboplatin, trastuzumab, pertuzumab and capecitabine. She came in for cycle 2 of cyclophosphamide. She had evidence of a clinical response in her cutaneous metastases. She was scheduled to have a pleurex catheter placed for chronic, recurrent pleural effusion. Breathing was at baseline (mild dyspnea). She received cyclophosphamide. Two days later the patient presented to clinic with complaint of weakness and shortness of breath, worsening over the last 2 days. The patient had not had much to eat or drink, this is typical of when she has had chemo before, similar to cycle 1 of cyclophosphamide. Urine appeared very concentrated and 1 liter of normal saline was administered in clinic along with oxygen. On exam she had a blood pressure of 113/70s, pulse 90s. Her left pleural effusion (on physical exam) was ~1/2 lung field. She had trace bipedal edema, which she also noted following her cycle 1 dose. She was advised to go to the emergency room to have the pleural effusion drained. The patient received SV-BR-1-GM following which she was stable with continued dyspnea and sent to the emergency room. In the emergency department, the patient was evaluated, and her initial intake vital signs showed a temperature of 35.4°C, a pulse of 71, a blood pressure of 97/72, a respiratory rate of 14, with 98% oxygen saturation on room air. On physical exam, she was noted to be distressed and tachycardic with decreased breath sounds on her left, consistent with the known malignant pleural effusion. Labs were remarkable for hyperkalemia, lactic acidosis, hypoproteinemia, transaminitis and leukocytosis. An initial chest x-ray was read as “Near complete white out of the left hemithorax…Heart size cannot be accurately assessed.” ECG findings included sinus tachycardia and low voltage QRS. Approximately 3 hours after her initial arrival to the emergency department, the subject went into pulseless electrical activity (PEA) arrest. CPR was initiated, the patient was intubated, and a left chest tube was placed. During the code, a limited transthoracic echocardiogram was obtained. With only subcostal windows, the patient was noted to have global left ventricular hypokinesis (ejection fraction estimated at 10%), “RV collapse during systole in the presence of a circumferential small volume pericardial effusion.” The patient had return of circulation with support of an epinephrine drip. A CT scan (without IV contrast) was obtained that was read as having “near complete consolidation of both lungs…Moderate to large pericardial effusion.” The patient remained on vasopressor medications in the ICU; however, she continued to decline clinically and ultimately

died. No autopsy was performed. The Investigator and the Sponsor both noted the event was unlikely related to study drug.

1.2. STUDY DESIGN

This study incorporates elements of Phase I design such as toxicity and immunological/allergy monitoring, which will measure the overall tolerability of the experimental therapy. In addition, Phase II elements such as clinical efficacy - determined as RECIST and iRECIST criteria - will be studied.

1.2.1. Study Purpose

The purpose of this study is to gather preliminary data to evaluate the safety, tolerability, and feasibility of targeted immunotherapy for advanced breast cancer with a special consideration for CNS metastasis using allogeneic breast tumor cell line transfected with the GM-CSF gene (SV-BR-1-GM). This experimental therapy will be evaluated in a small initial cohort of 25-40 subjects with qualifying stage IV breast cancer. SV-BR-1-GM is inoculated by intradermal injections with subsequent local injection of low-dose Interferon-alpha-2b (Merck).

1.2.2. Study Objectives

As this design incorporates elements of a preliminary safety/toxicity study, clinical response, duration of response, and survival are not primary endpoints of the protocol, but such data will be monitored for possible support of further research plans. Similarly, quality of life (QOL) will be assessed using a standardized questionnaire [73, 74] (See SF-36 Health Survey)

To evaluate the performance of the experimental therapy, the following objectives will be assessed.

1.2.2.1. Primary Objectives

To evaluate the number, frequency, duration, and relation of toxicity events to SV-BR-1-GM, as defined by CTCAE and additional tests as described in section 5.5.2.

1.2.2.2. Secondary Objectives

1. To evaluate tumor response:
   a. Objective response rate (ORR), defined as complete response (CR) or partial response (PR) per RECIST and iRECIST response criteria
   b. Non-progressive rate, defined as CR, PR or stable disease (SD) per RECIST and iRECIST
   c. Durability of response, by evaluating those patients eligible to complete the optional treatments from 9-12 months.

1.2.2.3. 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 data in support of further investigations blood and urine will be stored in a tissue repository for future analysis. Studies anticipated will include, but are not limited to histocompatibility characterization, levels of circulating cytokines antibodies and cell mediated immune responses.
3. To measure the quality of life (QOL) of participants and the effect the biological agent may have on the subjective sense of well-being. To measure changes in weight, performance status, and pain.

1.2.3. Rationale

A recent review describes a number of studies using cancer cell targeted immunotherapies genetically modified to produce various cytokines, including GM-CSF [75]. These reports add to the understanding of safety and tolerability for GM-CSF-transfected whole-cell targeted immunotherapies and reinforce the notion that the method of GM-CSF introduction appears to have several important advantages over subcutaneous injections of the exogenous cytokine: a) it is less labor-intensive, b) it is less likely to cause the side-effects associated with systemic GM-CSF injections, c) local cytokine concentration is more stable and long-lasting, and d) cytokine is directly released to activate APC at the site of targeted immunotherapy injection.

Thus, given the current data regarding GM-CSF secreting breast cancer cell line SV-BR-1-GM with several desirable features developed in our laboratory, we propose this clinical investigation. SV-BR-1-GM will be injected intradermally to potentiate activation of *in-situ* APC. Interferon-alpha-2b (Merck) will be used subsequently as an adjuvant, since it serves as a "danger signal" and has been shown to facilitate the maturation of APC precursors into functionally active dendritic cells [11]. Patients will be premedicated with low-dose cyclophosphamide because of its effect on T-regulatory cell activity [8, 9, 10, 76] and potential synergism with the targeted immunotherapy process by fostering cytokine responses, induction of MHC antigens on tumor cells or other mechanisms not yet identified [77].

1.2.4. Hypothesis

Based on preliminary results of the sponsor's previous studies of SV-BR-1-GM, it is hypothesized that this biological agent will be safe, well-tolerated, and clinically efficacious for metastatic breast cancer patients.

1.2.4.1. Success Measures

Success of the study in meeting the above hypothesis will be defined according to traditional FDA criteria. We will investigate the likelihood of objective responses and will apply the combined RECIST/iRECIST criteria as recently studied [78]. The key to success at this stage will be to compile an adequate pool of data to merit FDA recognition of "proof of principle" sufficient to warrant expansion to the next level of study (i.e. traditional Phase II and/or Phase III).

To this end, while the core success measure is safety and lack of toxicity, any of the following may be applied as Success Measures:

1. Objective clinical response as defined by RECIST 1.1 criteria or iRECIST criteria in 25% of patients.
2. Improvement in quality of life in 50% or more patients as evidenced by significant change in 1 or more scales in the SF-36 questionnaire.
3. Prolongation of disease-free and overall survival as compared with historical controls from reports of other salvage therapies in the published literature.

Evidence of development or amplification of immune responses, especially if correlating with prolongation of survival.

2. STUDY PLAN

2.1. TRIAL SITES

The investigational sites will screen patients and enroll within trial. The treatments will be administered to patients at the investigational sites. All scans will be obtained at the investigational sites and evaluated by the site PI. All blood tests will be performed at that the investigational sites or using major CLIA certified national laboratories. The results will be entered into the EDC.

2.2. STUDY POPULATION

2.2.1. Subjects

The subjects will be females age 18 or older, who are diagnosed with metastatic breast cancer and qualify via the inclusion and exclusion criteria. A sufficient number of subjects will be enrolled to assure a minimum of 10 for initial safety analysis and then expanded to 25-40 to complete the primary, secondary and exploratory end points. Patients who do not reach the initial on treatment tumor assessment may be replaced at the Sponsor's discretion.

2.2.2. Source of Subjects

New subjects may be enrolled into this study from several sources, including but not limited to:

1. From the investigational treatment sites, as qualifying patients present and are referred.
2. From physician referrals to the trial.
3. From the NCI-PDQ website.
4. From patient advocacy organizations or any other pertinent agencies.

2.2.3. Recruitment of Subjects

(See also section 5.1 for more details.) IRB-approved recruitment materials may be used to approach potential subjects during the screening period, as they present to the investigational treatment sites. These recruitment materials will also be provided to potential referring physicians, at their request. The consent form and attached study calendar; a brochure of frequently asked questions and answers; the enrollment forms are included in section 9.

2.3. ELIGIBILITY CRITERIA

2.3.1. Inclusion Criteria

1. Have histological confirmation of breast cancer with recurrent and/or metastatic lesions via investigational site.

**** Patients with new or progressive breast cancer metastatic to brain will be eligible provided:

a. There is no need for steroids and patients have not had steroids at least 2 weeks
b. No individual tumor size is >50 mm^3

c. ECOG status <3
d. Tumor is not impinging on Middle Cerebral Artery/speech-motor strip
e. If surgically debulked, must be healed from surgery and at least 3 weeks have elapsed since general anesthesia
f. Patients consent to MRI studies at 3-4 week intervals until evidence of tumor regression on at least 2 imaging studies. In no case, will the interval between MRI studies be longer than 3 months. MRI study may be introduced at any time should the patients develop new or clearly worsening symptoms and/or introduction of steroids
g. Must have received prior radiation therapy for brain metastases or be ineligible for radiation therapy

2. Have 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)
3. Be 18 years of age or older and female
4. Have expected survival of at least 4 months
5. Have adequate performance status (ECOG 0-2)
6. Patients may be maintained on hormonal therapy provided there is clear evidence of tumor progression
7. Have provided written informed consent.

2.3.2. Exclusion Criteria

1. Concurrent or recent chemotherapy (within 3 weeks), XRT within 1 week, may have had immunotherapy in the past (off within 3 weeks), or general anesthesia/major surgery (within 3 weeks). Patients must have recovered from all known or expected toxicities from previous treatment and passed a treatment-free "washout" period of 3 weeks before starting this program (8 weeks for persons receiving nitrosourea or mitomycin).

2. History of clinical hypersensitivity to GM-CSF, Interferon-alpha-2b (Merck), beef, or to any components used in the preparation of the experimental therapy.

3. BUN >30 in conjunction with a creatinine >2.

4. Absolute granulocyte count < 1000; platelets <100,000.

5. Bilirubin >2.0; alkaline phosphatase >5x upper limit of normal (ULN); ALT/AST >2x ULN.

6. Proteinuria >1+ on urinalysis or >1 gm/24hr.

7. Left ventricular ejection fraction (LVEF as determined by cardiac echo or MUGA scan) below the normal limits of the institutions specific testing range. This assessment may be repeated once at the discretion of the Investigator with the approval of the Sponsor.

8. New York Heart Association stage 3 or 4 cardiac disease.

9. A pleural or pericardial effusion of moderate severity or worse.

10. Any woman of childbearing potential, unless she:
    a. Agrees to take measures to avoid becoming pregnant during the study and
    b. Has a negative serum pregnancy test within 7 days prior to starting treatment.

11. Women who are pregnant or nursing.

12. Patients with concurrent second malignancy. Persons with previous malignancies effectively treated and not requiring treatment for >24 months are eligible, provided there is unambiguous documentation that current local recurrence or metastatic site represents recurrence of the primary breast malignancy.

13. Patients who are HIV positive (by self-report) or have clinical or laboratory features indicative of AIDS.

14. Patients who require systemic steroids at a dose equivalent of >10 mg/day of prednisone. Beta-blocker therapy, while not exclusionary, is discouraged and alternatives should be sought if possible. The beta-blocker might compromise use of epinephrine for the rare possibility of anaphylaxis. Anticoagulants must be approved by the Investigator with notification of the Sponsor.

15. Patients who are on treatment for rheumatological or autoimmune disease unless approved by the Investigator in consultation with the Sponsor (e.g., as for replacement therapy for autoimmune thyroiditis or diabetes).

16. Patients with severe psychiatric disorders (e.g., schizophrenia, bipolar, or borderline personality disorder) or other clinically progressive major medical problems, unless approved by the PI.

17. Male breast cancer patients.

18. Patients may not be on a concurrent clinical trial, unless approved by PI.

2.4. DURATION OF PARTICIPATION

1. **Initial screening and enrollment** (approximately 1-4 weeks): The actual time it will take for introduction of the study to prospective subjects, the consent process, and screening & enrollment procedures is difficult to estimate due to clinical and scheduling considerations.

2. **Initial phase:** Participants will receive 3 cycles of SV-BR-1-GM at 2-week intervals. The initial phase is expected to last about 1 month.

3. **Monthly maintenance phase:** Subjects will receive SV-BR-1-GM cycles monthly for 6 months (8 total cycles). Initial reimaging, laboratory evaluation and clinical evaluation will be performed at 2-3 months from initiation between SV-BR-1-GM cycles 4 and 6. Similar imaging re-evaluation will take place after every 3 months to identify progressive disease, to evaluate any off-study clinical criteria, and to investigate any possible clinical or immunological responses. Imaging may be performed more frequently, at the discretion of the Investigator in consultation with the Sponsor. Copies of all imaging reports should be deidentified and provided to the Sponsor or their designate for entry into the database.

4. **Optional monthly maintenance treatments:** Subjects that have completed 8 cycles, have a non-progressive response, and desire to continue on treatment have the option to receive an additional 6 months of treatment (6 cycles) for a total of 12 months of treatment (14 cycles in-total). They will have additional imaging, laboratory evaluation and clinical evaluation at month 9 after the 11^{th} cycle. If they continue to have a non-progressive response and desire to stay on treatment, they may continue out the 12 months of treatment.

Total duration: Each subject's active participation in the above phases combined is expected to last a total of approximately 6-12 months, allowing for "real life" variations in scheduling.

3. EXPERIMENTAL TREATMENT REGIMEN

3.1. GENERAL INFORMATION

This is a preliminary safety/toxicity study, clinical response, duration of response, and survival data are also being collected. Quality of life is assessed by a standardized questionnaire (SF-36 Health Survey). The protocol begins with characterization of the patients' clinical and immunological status. The experimental part of the study employs intradermal immunization with irradiated, GM-CSF-producing breast cancer whole-cell targeted immunotherapy SV-BR-1-GM, pretreatment with low-dose cyclophosphamide, and boosting with an injection of low-dose Interferon-alpha-2b (Merck) to the inoculation site after 2 and 4 days. The study concludes with follow-up for restaging after the 6-12 months of treatment.

3.2. SUBJECT SCREENING

Subjects will undergo staging and baseline studies within about 14 days of starting treatment; within 28 days for radiographic studies. The screening window may be extended to 40 days with the approval of the Sponsor. See sections 5.3 and 5.5 for more detailed information.

3.3. SV-BR-1-GM CYCLES

SV-BR-1-GM administration cycle begins when low-dose cyclophosphamide is given via intravenous infusion 2-3 days before SV-BR-1-GM. Low-dose cyclophosphamide may have multiple modes of action, including the down-regulation of immune regulatory T-cell activity [8,9], induction of type 1 Interferon-alpha-2b (Merck) [10], up-regulation of MHC antigens [79], reversal of tolerance via up-regulation of tumor-specific CD4+ helper activity [80], and/or by other mechanisms not yet studied. Following injection of SV-BR-1-GM, clinical evaluation and Interferon-alpha-2b (Merck) -α booster injection *in situ* at the inoculation site occurs 2 days and 4 days later. Interferon-alpha-2b (Merck) is included particularly because of its effect in augmenting dendritic cell maturation [11, 81, 82]

Pre- SV-BR-1-GM Regimen:

Cyclophosphamide (Cytoxan) 300 mg/m^2 I.V., 1x only, will be given 2-3 days before each SV-BR-1-GM dose, with an antiemetic of the provider's choice (steroids prohibited). To simplify, this event will also include the phlebotomy, which should occur prior to the cyclophosphamide infusion. See Table 2. If the patient is not tolerating the cyclophosphamide, a lower dose may be used (e.g. 200 or 150 mg/m^2) or it may be withheld, but only with the Sponsor's approval.

SV-BR-1-GM Day Standard Operating Procedures:

a) Inquire regarding events of past weeks, change in medications, pain scale, ECOG scale, and review of systems.
b) Check SV-BR-1-GM injection sites.
c) Perform immediate and delayed-type hypersensitivity (DTH) skin testing by intradermal injection of BriaTest™ (irradiated SV-BR-1 parent cells) or with SV-BR-1-GM. BriaTest™ or SV-BR-1-GM will be used to evaluate potential immediate hypersensitivity and DTH.

Observe about 20 minutes for acute hypersensitivity to the SV-BR-1 parent cells or SV-BR-1-GM. Any evidence of immediate hypersensitivity to the SV-BR-1 parent cells or to the test dose of SV-BR-1-GM precludes dosing with the full dose of SV-BR-1-GM.

d) Anergy testing with Candida antigen will also be performed prior to dosing on cycles 1, 3, 6, 9, 12. Candida antigen (Candin, 0.1 mL) will be injected intradermally into the forearm and evaluated 2 days (±1 day) later to evaluate for anergy.
e) Inject SV-BR-1-GM 0.5 ml intra-dermally into thighs and upper back. Monitor patients for 60 minutes. Vital signs will be assessed and medical attention will be warranted if unstable.

SV-BR-1-GM Preparation & Inoculation Regimen:

Each SV-BR-1-GM inoculation will be administered via intra-dermal injection at the investigational sites. Subjects will receive 15-25 x 10^6 irradiated transfected breast tumor cells in a total volume of 2.0 ml Ringer's lactate. SV-BR-1-GM cells will be irradiated to 20,000 cGy (dose applied previously), or to an alternative dose ensuring cell replication incompetency, with an approved Cesium source or alternatively in Varian Linac IX, medically approved for radiation therapy. The liquid formulation of SV-BR-1-GM and skin test material (BriaTest™ or SV-BR-1-GM) should be kept under temperature controlled conditions (2-8° C) until ready for use (i.e. when the results of all release testing is available). If the frozen formulations are used, SV-BR-1-GM should be thawed at room temperature and then kept under temperature controlled conditions (2-8° C) until ready for use.

Prior to SV-BR-1-GM administration, both the skin test and the final SV-BR-1-GM preparations will be gram stained and tested for endotoxin at the sponsor's designated laboratory. The remainder will be stored frozen at –80° C for future reference. No preparations will be injected if the gram stain is suspicious for bacterial or other contamination or if the endotoxin test is positive. Nothing will be administered unless and until there is review that there is nothing positive on the gram stain and the endotoxin test is negative.

SV-BR-1-GM will be divided into aliquots and prepared with coded study labels "Investigational Use Only", and hand-delivered or shipped overnight to the clinical site on the day of the scheduled inoculation. At the Investigator's site, the BriaTest™ and/or SV-BR-1-GM will be thawed if frozen. SV-BR-1-GM is stable up to 24 hours at 2 – 8 °C and should not be used more than 24 hours following the conclusion of irradiation for the liquid formulation. SV-BR-1-GM will be delivered in cryovials and should be drawn into syringe(s) through a large bore (18 gauge or larger) needle. It may be back-filled into 1 mL syringes for injection, or could be directly injected following switching to a smaller gauge needle (e.g. 27 gauge). SV-BR-1-GM will be injected intra-dermally; one each into the anterior skin of the subject's right and left thighs and over the right and left upper back. Application of anesthetic lidocaine crème may be used if necessary for control of local pain before inoculation. Subjects will be monitored for 60 minutes with vital signs performed at least every 15 minutes, or more frequently if clinically indicated. See the Pharmacy Manual for additional details.

After at least 10 subjects have been treated with this regimen, at the Sponsor's discretion and in consultation with the investigator, the dose of SV-BR-1-GM may be escalated to 30-50 x 10^6 irradiated transfected breast tumor cells in a cohort of 6 or more patients. This dose will not be

exceeded without further protocol amendment, FDA notification and IRB approval. At the Sponsor's discretion and in consultation with the investigator, the dose of SV-BR-1-GM may also be decreased to 5-15 x 10^6 irradiated transfected breast tumor cells in a cohort of 6 or more patients. If, after dosing the first 10 patients at a dose of 15-25 x 10^6 irradiated transfected breast tumor cells, grade 2 or higher toxicity at least possibly related to SV-BR-1-GM inoculation is seen in at least 30% of patients, the dose will be decreased to 5-15 x 10^6 irradiated transfected breast tumor cells for subsequent patients.

Post-Inoculation Regimen:

Two days (±1 day) after SV-BR-1-GM, and again 4 days (±1 day) later after SV-BR-1-GM, the patient will return to the principal investigator's office to receive 10,000 U of Interferon-alpha-2b (Merck) in 0.1 ml saline. This may be prepared as follows (alternative methods also permissible):

1) Retrieve vial of Intron A liquid (conc. = 10 million IU/mL)
2) Withdraw 0.5 mL (5 million IU) from the vial with a syringe
3) Dilute with 49.5 mL NS + 0.9% benzyl alcohol in a sterile empty vial (conc. = 100,000 IU/mL)
4) Withdraw 0.1 mL (10,000 IU) per syringe (prepare 4 syringes in total per protocol)
5) Store at 2-8° C. Stable for up to 28 days.

One alternative method is shown here:

1) Retrieve vial of Intron A powder, 10 million IU/ml in bottle.
2) Add 1.0 ml NS + 0.9% benzyl alcohol (conc 10 mil IU/ml)
3) Dilute to 100 ml with NS + 0.9% benzyl alcohol (conc100,000 IU/ml)
4) Aliquot to syringes 0.10 ml (=10,000 IU)
5) Store at 2-8° C. Stable for up to 28 days.

These will also be injected intra-dermally to each SV-BR-1-GM inoculation site, beneath the thickest area. Again, subjects will be observed about 20 minutes. The DTH/anergy response will also be recorded in the EDC at the 2 days (±1 day) visit.

General Regimen for Adverse Reactions:

1. **Acute -** Contingent on clinical features, the following protocol will inform the management of any acute hypersensitivity rxn., to be adhered to or modified according to the treating physician.

   --Fever, chills, rigors: acetaminophen 1000 mg po
   --Urticaria (hives), itching, facial flushing: IV diphenhydramine 50 mg.
   if no improvement within 5 minutes, IV hydrocortisone 100 mg.
   repeat IV diphenhydramine 50 mg, 0.2 – 0.5 mL epinephrine 1:1000 subcutaneous
   --Hypotension, wheezing, shortness of breath, lip, tongue swelling

Place pulse oximeter; if O_2 saturation <92%, start O_2 by nasal cannula 2 l/min
NS 150ml/min,
Rx 0.2 – 0.5 mL epinephrine 1:1000 subcutaneous, IV diphenhydramine 50mg, 100 mg hydrocortisone

2. Chronic – treatment as determined by the treating physician.

In the case of grade 3 or greater localized toxicity (e.g., ulcer formation) further dose inoculation will not occur.

It is expected that all experimental treatment procedures will be performed in the principal investigator's office, and hospitalization is not expected unless complications develop. Treatment will be administered with appropriate medical supervision and the close availability of support measures.

Subsequent SV-BR-1-GM Cycles:

SV-BR-1-GM Cycles 2 and 3 will occur at 2-week intervals from initiation of treatment for a total of 3 cycles. Cycle 4 will be initiated one month later, provided there has not been undue toxicity (defined under Treatment Plan, Toxicity). Subsequent cycles will then occur monthly; with restaging every 3 months.

For example, restaging would occur at month 3, after completion of 5 SV-BR-1-GM cycles. Patients with progressive disease should go off treatment after 5 SV-BR-1-GM cycles, or earlier if needed as per the PI. Patients without progressive disease may remain on treatment and will be restaged after completion of SV-BR-1-GM cycles 6, 7, 8 after 6 months. If they remain non-progressive they continue for another 3 cycles (1 per month), followed by restaging at 9 months (cycles 9, 10, 11). Again, if they remain non-progressive they may continue for another 3 months (cycles 12, 13, 14) followed by final staging. Thus, the program totals 12 months of SV-BR-1-GM inoculations. Refer to the study calendar below (Table 2) for a complete schedule.

Table 2: Study Calendar (SV-BR-1-GM Cycles)

STUDY EVENT	Eval	Inj	Inj	Inj	Inj	Inj	Eval	Inj	Inj	Inj	Eval	Eval
Visits	Baseline Eval.	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Initial Treatment Eval.	Cycle 6 9 12	Cycle 7 10 13	Cycle 8 11 14	Re-Eval (after every 3 cycles)	Off Tx Eval (after Cycle 14 or when off-study)
Week/Month of Study	-2wk	1	3wk	5wk	2mon	3mon	Between 2-4mon	4, 7, 10 mon	5, 8, 11 mon	6, 9, 12 mon	After 6, 9 mon	After 12 mon
COMPLETE PHYSICAL EXAM (8)	X						X				X	X
Vital Signs & Wt Status	X	X	X	X	X	X	X	X	X	X	X	X
Review of Systems	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Form	X	X	X	X	X	X	X	X	X	X	X	X
Abbrev. Physical Exam (8)		X	X	X	X	X		X	X	X		
LABORATORY												
Serum/Plasma (1 red top ~8ml & 1 purple top ~8 ml)	X	X					X				X	X
PBL (3 yellow top ~24 ml)	X	X					X				X	X
CBC & Diff.	X	X	X	X	X	X	X	X	X	X	X	X
CMP, GGT, LDH, Uric Acid (2)	X	X	X	X	X	X	X	X	X	X	X	X
PT, aPTT, INR (2)	X	X					X				X	X
Serum Pregnancy Test (7)	X											
T&B Subsets	X	X					X				X	X
Serologic Markers (2)	X	X					X				X	X
Urinalysis (6)	X	X					X				X	X
2 CellSave Preservation Tubes (~10 ml each)		X					X				X	X
HLA Typing (buccal swab)	X											
DTH Skin Test (4)		X	X	X	X	X		X	X	X		
Anergy (Candin) (4)		X		X				X				
Cardiac Assessments (9)	X						X				X	X
TUMOR ASSESSMENT RADIOLOGY (1)	X						X				X	X
TREATMENT												
Cyclophosphamide		X	X	X	X	X		X	X	X		
SV-BR-1-GM Inject (4)		X	X	X	X	X		X	X	X		
Interferon Injection #1 (5)		X	X	X	X	X		X	X	X		
Interferon Injection #2 (5)		X	X	X	X	X		X	X	X		
DATA SAFETY & EVALS FOR AEs		X	X	X	X	X	X	X	X	X	X	X

Notes:

1. Radiology Procedures: Baseline studies to be performed within 28 days of beginning clinical trial (as clinically indicated for staging). CT of: chest, abdomen, pelvis; isotope bone scan; other X-Rays; PET scan; mammogram; (ultrasound/MRI scans as needed for disease assessment and/or at the discretion of the investigator). These will be repeated between SV-BR-1-GM cycles 4 and 6, and then every 3 months or more frequently at the discretion of the Investigator in consultation with the Sponsor. Patients with disease progression should progress to the Off Tx Evaluation.
2. All blood to be drawn on arrival for cyclophosphamide infusion; if overlooked, may draw before skin tests, but must be annotated clearly. Comprehensive Metabolic Profile (CMP), GGT, LDH, and Uric Acid to be done each visit. Coagulation studies (PT, aPTT, INR) should be performed every 3 months as noted. These or other laboratory evaluations may occur more frequently for responsible patient care at the discretion of the investigator. Serological markers include: CEA; CA 27.29 (or CA 15-3 if preferred by the Investigator).
3. Day 1 of each cycle is the day of SV-BR-1-GM injection.
4. DTH skin test will be with $1.0 \pm 0.2 \times 10^6$ irradiated BriaTest™ (SV-BR-1) cells or 1.0 ± 0.2

x 10^6 irradiated SV-BR-1-GM cells intradermally in the forearm. See Sec. 3.3.

5. Interferon-alpha-2b (Merck) injection is done 2 (±1) days and 4 (±1) days after SV-BR-1-GM injection.
6. Aliquot of urine to be archived with each U/A
7. For women of childbearing potential, a pregnancy test will be done within 7 days of starting SV-BR-1-GM.
8. Complete physical exam will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. Brief physical exam will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. Abbreviated physical exam is needed for Cycle 1 only if not performed within the past 2 weeks.
9. Cardiac assessments will include baseline ECG, cardiac troponin (cTn), NT-proBNP and an estimation of left ventricular ejection fraction (LVEF) by either cardiac echo or MUGA scan. The ECG and estimate of LVEF (by the same method) will be performed after 3, 6 and 12 months on study if the subject remains asymptomatic, or earlier if a patient becomes symptomatic. LVEF assessment may be repeated once at the discretion of the Investigator with the approval of the Sponsor.

4. RISKS, BENEFITS, & RISK MANAGEMENT

Trial subjects will be monitored closely for any side effects and will be encouraged and expected to report any new symptoms or developments to the principal investigator.

4.1. PHYSICAL RISKS

SV-BR-1-GM: Allergic reactions, local pain, redness, or itch, local infection or other infections; tumor enhancement; allergy to the SV-BR-1-GM, cross-reactive allergy to food or medicines; autoimmune disease.

Cyclophosphamide: Low-dose cyclophosphamide (Cytoxan) is sometimes associated with nausea, loss of appetite, or vomiting, constipation. Side effects of the higher, conventional doses include hair loss, fall in blood counts (which can lead to fatigue, increased risk of infection), and bladder irritation.

Interferon-alpha-2b (Merck): The dose of Interferon-alpha-2b (Merck) used here (10,000 U) is a tiny fraction of the usual amount used clinically (1 million U or more). Possible side effects include itching, inflammation, pain, or local infection at the injection puncture site.

GM-CSF: Since only small amounts of GM-CSF are released at the SV-BR-1-GM inoculation site, side effects reported in other studies with much larger doses are not expected. Larger clinical doses have produced flu-like symptoms or local reaction such as redness or itching at the site of the injection, acute allergic reactions to the lymphokine, and exacerbation of underlying heart, lung, or liver problems.

Combinations of Agents: SV-BR-1-GM has been safely administered in combination with pre-treatment cyclophosphamide and post-treatment interferon alpha as noted above. No adverse events outside of those expected from the individual agents were seen. Additional, unexpected side effects may be seen.

4.2. NONPHYSICAL RISKS

Non-physical risks may include increased time commitments and travel considerations, financial implications, loss of privacy, or problems with insurability. Participation on this protocol requires termination of previous treatments and excludes concomitant treatments by other standard or investigational programs.

4.3. ADVERSE EVENTS

4.3.1. Definitions and Reporting

For the purposes of this Protocol, an adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms,

are considered clinically meaningful, require therapy (e.g., hematologic abnormality that requires transfusion), or require changes in the study drug(s).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the CRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the CRF. Adverse event monitoring should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the CTCAE version 4.03. The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).
  - Note that when SV-BR-1-GM is used in combination with other agents (e.g. cyclophosphamide, interferon-α), the relationship to study drug can be assessed for SV-BR-1-GM alone, the other study medications alone, or the combination of agents.
- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (e.g., none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (e.g., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 8.3.2.

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the CRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

4.4. LABORATORY TEST ABNORMALITES

4.4.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the CRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

4.5. SERIOUS ADVERSE EVENTS

4.5.1. Definitions and Reporting

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (i.e., immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (i.e., defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition. Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

- Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

The Sponsor will notify FDA and all participating investigators in an IND safety report of potential serious risks identified, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after determination that the information qualifies for reporting, as delineated in CFR 312.32 (available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32). Unexpected fatal or life-threatening suspected adverse reaction reports. The Sponsor will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Note that when SV-BR-1-GM is used in combination with other agents (e.g. cyclophosphamide, interferon-α, ipilimumab, pembrolizumab), the relationship to study drug can be assessed for SV-BR-1-GM alone, the other study medications alone, or the combination of agents.

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of

the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate may urgently require further information from the investigator for reporting to health authorities.

The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

4.6. RESPONSE TO ADVERSE EVENTS

All adverse events will be recorded on the Adverse Event Form. Development of treatment related Grade IV toxicity will truncate all new subject accrual until further review by the medical monitor, IRB and FDA as appropriate. Treatment-related Grade III allergy/hypersensitivity will truncate further inoculations to any particular subject. The first three patients will be enrolled sequentially, with at least 2 weeks between patients. After 10 patients are enrolled a safety analysis will be performed. If no significant toxicity has been reported, an additional cohort of 15-30 participants (to a total of 25-40) may be enrolled to evaluate the primary, secondary and exploratory end points.

If any subjects show an unanticipated abnormality on any lab assay or screening procedure, clinical management of their condition will take precedent. Results of testing will be provided to their physician(s) with appropriate medical release.

4.6.1. During SV-BR-1-GM Administration

1. ***Pain and/or anxiety***: Subjects will be closely monitored for their reaction to SV-BR-1-GM administration, including any pain at the injection site, general anxiety or discomfort. Appropriate rest periods will be offered, and subjects always have the right to withdraw from the study at any time and/or refuse an injection.
2. ***Other adverse events***: Unanticipated adverse events should be managed as clinically appropriate, and recorded on the Adverse Event Form.

4.6.2. After the SV-BR-1-GM Administration

After SV-BR-1-GM inoculation, the subject will be monitored for 60 minutes for any adverse reaction to the SV-BR-1-GM. Unanticipated adverse events should be managed as clinically appropriate, and recorded on the Adverse Event Form.

4.6.3. In Case of Injury

No funds have been provided or set aside in case of injury to a subject. Each subject (primarily their insurance or Medicare) will be responsible for usual and customary fees regarding the procedures, supplies used in this study, and office visits, with the exception of the experimental therapy. There will be no charges for preparation or administration of SV-BR-1-GM, but there will be routine charges for an office visit, imaging, laboratory tests, etc.

4.6.4. Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI) is to be reported on the SAE form and timelines for submission and processing are expected to be the same as a reported SAE. Adverse Events of Special Interest include the following:

- New or worsening Autoimmune Disease
- Major cutaneous reactions at the inoculation sites (e.g., ulcers, necrosis)
- Allergic reactions to SV-BR-1-GM
- Cardiac events

4.7. BENEFIT TO SUBJECTS & OTHERS

This is a Phase I/IIa safety and efficacy study of an experimental treatment that has not yet been proven. No direct benefits to subjects can be anticipated. Even though this experimental treatment is based on current medical science theories, it is not possible to predict the outcome in advance. Possible benefits may include improvement in immune function or possible tumor regression, or possible improvement in time to progression or survival after treatment. However, each person is unique and results are not predictable.

5. STUDY PROCEDURES, METHODS, AND MATERIALS

5.1. RECRUITMENT

It is expected that patients will sometimes be referred by clinicians who know the sponsor or affiliated investigators, or they may self-refer after an internet search. The sponsor will refer all patient inquiries to an appropriate principal investigator.

Potential participants will be informed that this program is experimental and that an evaluation on site is necessary to make the final decision on whether a patient qualifies for the program. In addition, each potential participant is to be clearly informed that travel costs and other expenses associated with the screening, eligibility, and study procedures will not be compensated without pre-approval of the Sponsor. Prospective participants will be denied participation if all eligibility criteria are not met or, if after screening and evaluation the principal investigator or the patient's personal physician feels some other therapy is more appropriate.

5.2. CONSENT PROCESS

a) The investigational trial site staff will explain the study, its procedures, and the consent documents to patients.
b) Potential participants will be given an opportunity to read the consent documents, to have their questions answered to their satisfaction, and to defer a decision, perhaps to discuss study participation with their physician or significant others.
c) It will be carefully explained to participants that they may withdraw from participation at any time, without prejudice or jeopardy to their standard medical care.
d) In all cases, prior to initiation of treatment, participants are again queried regarding their understanding of the program, or any unresolved issues. A copy of the consent form will be provided to the participant, and this is to be noted within the electronic case report form (eCRF).

5.3. SCREENING PROCESS

Written informed consent will be obtained before any screening procedures are initiated. Study staff may explain the study to participants and ascertain presumptive eligibility. Multiple visits may be conducted to complete all required procedures if necessary. Due to the delay in receiving the results of tests, the final eligibility decision cannot be made during the participant’s initial screening visit.

a) After review of all screening information, an entry will be made in the Screening & Enrollment Log for all participants who consent to be in the study, whether or not they qualify after the screening procedures.

b) If any participant is determined to meet preliminary eligibility criteria, and expresses willingness to continue with the study, she will proceed. Detailed instructions, study-specific procedures and study calendar will again be explained to qualified participant.

c) If any participant is determined to be ineligible, she will be informed by the study staff of the reason(s) for ineligibility.

5.4. WITHDRAWAL and TERMINATION CRITERIA

5.4.1. Individual Subject Withdrawal Criteria

1. Criteria - Any individual subject can be withdrawn from the study if any of the following occurs:
   a) The subject may request at any time to withdraw from the study, with no prejudice to her medical care at the principal investigator's practice.
   b) The subject is unable to reliably adhere to the study procedures.
   c) The subject exhibits extreme anxiety during the treatment.
   d) Staff members are unable to contact the subject or proxy to collect post-procedure information will account as withdrawal.

2. After providing 'adequate trial' with sufficient time and doses, experimental therapy will be terminated in a subject with significantly progressive disease.

3. In addition, experimental therapy will be terminated in a subject at the discretion of the sponsor or principal investigator if:
   a) The patient/subject demonstrates evidence of progressive disease as per RECIST and iRECIST criteria.
   b) Grade III or IV toxicity of any kind occurs, or
   c) Autoimmune disease (validated) of any toxicity level.

4. Subjects MUST be withdrawn from dosing for any of the following:
   a) Any grade 3 or greater NCI CTC v. 4.03 toxicity at least possibly related to study agent.
   b) Any grade 2 or greater hypersensitivity reaction.
   c) If LVEF drops >20% or is below facility limits of normal or the patient becomes symptomatic of CHF and requires treatment. LVEF assessment may be repeated once at the discretion of the Investigator with the approval of the Sponsor.

5.4.2. Study Termination Criteria

The study will be terminated if any of the following occur:
   a) Any death at least possibly related to the study drug.
   b) 2 or more grade 4 events at least possibly related to the study drug.

If either of these occur, recruitment will be halted and dosing of all subjects paused while the case(s) are investigated. Following discussions with the IRB/Ethics Committee and with regulatory authorities, the protocol may be amended. The study may be restarted only with the approval of the IRB/Ethics Committee and regulatory authorities.

5.5. STUDY TESTS & PROCEDURES

5.5.1. General Considerations

The pre-study tests (see section 5.5.2.1) should be obtained prior to enrollment in accordance with good medical practice. Results do not necessarily determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician after consultation with the Medical Monitor. Further review and consultation with the Institutional Review Board is anticipated if there are significant deviations from the values of these tests, from ongoing monitoring, and/or changes in clinical status.

1. Subject safety and comfort are of first priority and unexpected events may occur, to be responded to according to the physician's judgment and community standards of clinical practice.

2. Subjects will undergo imaging studies within 28 days of starting treatment; baseline laboratory studies within 14 days. (See also Study Calendar.)

5.5.2. Study Tests & Evaluations

5.5.2.1. Pre-Study Testing and Ongoing Monitoring

1. Focused medical & social history (screening).
2. Complete physical exam, including vital signs.
3. Cardiac assessments will include baseline ECG, cardiac troponin (cTn), NT-proBNP and an estimation of left ventricular ejection fraction (LVEF) by either cardiac echo or MUGA scan. LVEF assessment may be repeated once at the discretion of the Investigator with the approval of the Sponsor.
4. CBC, differential, platelets, T and B subsets, comprehensive metabolic biochemical profile, LDH, GGT, and uric acid, at each visit, or as clinically indicated. Coagulation studies (PT, aPTT and INR) and urinalysis at baseline, Cycle 1, and then every 3 months. All labs during treatment should be drawn prior to administration of cyclophosphamide. Additional blood samples will be collected during the same phlebotomy procedures, for storage in the repository. (See Laboratory Manual)
5. HLA profile – to be obtained from a buccal swab. Patients should gargle with water and then fast until the buccal swab is collected approximately 30 minutes later. Please handle with gloves to avoid contamination.
6. Quality of Life Questionnaire SF-36.
7. ECOG scale.
8. CT scan chest, abdomen and pelvis (or PET scan at the discretion of the PI) at baseline (within 28 days of initiation of treatment), at initial treatment evaluation, after 3 monthly maintenance inoculations, and after study conclusion. Chest X-ray at baseline is desirable but not required if patient is getting CT study.
9. Isotope bone scan, and/or selected MRI if clinical suspicion of bone metastases.
10. MRI or mammogram of the breast at baseline; if positive repeated at 3-months and subsequent evaluations; PET is desirable but not required. (This is not applicable if the patient has had a complete mastectomy).

11. CEA and CA 27.29 (or CA 15-3 if preferred by the Investigator).
12. Brain scan MRI or CT technique if clinical indication of neurological symptoms.
13. Serum beta-HCG pregnancy test within 7 days before starting treatment for women of childbearing potential.
14. Immunohistological and FISH evaluation, if not already performed by a referring physician, of HER2/neu expression from whatever previous biopsy was diagnostic of cancer metastases.
15. If tumor tissue is available for additional testing, it may be sent for evaluation of additional markers such as PDL1, PRAME, HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DP, and/or HLA-DQ.
16. If malignant fluids (e.g. pleural fluid, ascites) or tumor tissue (e.g. from biopsies) are available, unused or unneeded portions may be collected and archived for future research, provided nothing is done to compromise good clinical practice for the intended diagnostic evaluation. Possible research may involve characterization studies (e.g. antigenicity, genomic evaluations, transcriptome or proteome analyses) or establishment of cell lines.

During the initial phase of experimental therapy, participants will get SV-BR-1-GM injected and closely observed about every 2 weeks at the investigational sites. Subsequent inoculations occur at monthly intervals. Data will be recorded on eCRF for safety monitoring and/or relevant toxicity evaluation.

5.5.2.2. Immunological/Allergy Monitoring

Anergy Evaluation: Antigen preparations and suppliers as determined by availability: Candida 0.10 ml (Candin: Niesen Biosciences, San Diego, CA. nielsenbio.com). The erythema and induration reaction will be measured and captured in the EDC at approximately 2 days (to coincide with the Interferon-alpha-2b injection appointment).

Delayed-type hypersensitivity (DTH) reaction - tumor-specific: An aliquot of 1.0 (± 0.2) x 10^6 non-transfected irradiated SV-BR-1 tumor cells or 1.0 (± 0.2) x 10^6 irradiated SV-BR-1-GM cells, and, if available, irradiated autologous tumor cells, prepared identically as original source of SV-BR-1 (BriaTest™), each in 0.1ml of LRS will be injected intra-dermally into the patient's arm on the day of SV-BR-1-GM injection.

At the time of testing, the cutaneous tumor-cell injection will be observed for the possibility of immediate hypersensitivity reactions, and the patient will be monitored for 20 minutes or more before proceeding with full dose SV-BR-1-GM injection. Any evidence of immediate hypersensitivity, such a urticaria, will preclude administration of full dose SV-BR-1-GM. The erythema and induration reaction will also be measured approximately 2 days later (to coincide with the Interferon-alpha-2b (Merck) injection appointment) and captured in the EDC.

5.5.2.3. Cutaneous Monitoring Criteria

Immediate hypersensitivity is defined as a 2x increase of the two largest measured diameters of the initial injection wheal, occurring within 20 minutes, or the development of systemic symptoms of wheezing, additional zones of urticaria remote from the injection site, or generalized pruritus. Immediate hypersensitivity precludes further SV-BR-1-GM treatment on

that visit, will be treated as appropriate in the clinical judgment of the clinician, and evaluation by an allergist will be encouraged. Further SV-BR-1-GM inoculations are still permissible contingent on recommendations by a board-certified allergist

The presence of an immediate reaction to tumor SV-BR-1-GM may not imply absence of desired delayed-type cell-mediated immune responses. It is not known whether further tumor SV-BR-1-GM immunization might or might not down-regulate the Type I hypersensitivity, analogous to clinical allergy desensitization.

Delayed type hypersensitivity will be assessed at about 2 days after injection. The two largest diameters of induration and erythema will be measured in our clinic by the PI, nurse, or other clinical staff, and each type of response will be evaluated independently. While most investigators consider induration as the relevant response, a recent paper involving melanoma demonstrated improved survival was highly correlated to skin test responses as measured by erythema [84]

5.5.2.4. Tumor and SV-BR-1-GM Specific Immunological Response

Serum antibodies to SV-BR-I whole cell antigens, and to HER2/ neu: The antibody titers will be determined by ELISA according to methods described in laboratory SOPs.

Peripheral blood antigen-reactive T cells to SV-BR-I cell: The antigen reactive T cells will be determined by flow cytometry or by other tests (e.g. ELISpot).

5.5.2.5. Collection of Biological Specimens for Ongoing Research

Biological specimens will be collected from patients who provide additional consent using the form in section 9.1.3. Collection will take place during study visits according to the schedule in Table 2 and will take place in the offices of investigational institutions. Whenever possible, specimen collection will take place during the same venipuncture procedures as for the toxicity studies, so that only one blood draw procedure need be performed during any visit. Urine will be collected via urine specimen cup using the clean catch method.

Specimens to be collected include:

- 1 red top (~8ml), 1 purple top (~8 ml), and 3 yellow top (citrate) vacutainer tubes (3x ~8 ml).
- 2 CellSave Preservative Tubes (https://www.cellsearchctc.com/product-systems-overview/cellsave-preservative-tubes) (~10 ml each) – One tube may be collected at the Investigator's discretion if necessary to protect patient safety.
- Urine specimen cup (~100ml or larger).

Phlebotomy of peripheral blood will be collected by credentialed staff (RN, LVN, etc.) according to community practice. Serum (approximately 8 ml) will be collected in commercially available vacuum tubes (red top) used for serum collection, purple top tube (approximately 8ml) used for plasma and an additional amount will be collected in commercially available citrate vacuum tubes for harvest of peripheral blood lymphocytes (approximately 24ml) and for evaluation of

circulating tumor cells and related markers (approximately 20ml, or 10 ml at the discretion of the investigator). Malignant fluids (if available) will be placed in heparinized tubes or other suitable vessels for harvest of malignant cells.

Handling of the specimens after collection will follow the procedures found in the separate Laboratory Manual for future research protocols.

5.5.3. Goals of Immunological/Allergy Monitoring

Tumor-specific immunological response: ERBB2 (HER-2/neu) and the cancer/testis antigen PRAME are expressed in the SV-BR-1-GM cell line (M. Lacher and C. Wiseman; American Association for Cancer Research annual meeting, 2016, New Orleans). While it is expected that other relevant antigens may be present as well, the presence of at least these antigens will provide the study with candidate antigens to correlate with clinical benefit. We will try to evaluate the generation of immune responses against the tumor cell-line, and, if such responses are present, identify if directed against HER-2/neu or non-HER-2/neu epitopes. Clinical immunotherapy studies using purified HER-2/neu antigens have reported up-regulation of T-cell responses to antigens quite unrelated to those used for immunization, the phenomenon of "epitope spreading," [56] and this phenomenon may or may not be identified in this trial. We will collect information regarding subjects' HER-2/neu status and treatment with trastuzumab for data analysis, but do not exclude or stratify otherwise qualified breast cancer subjects by these criteria.

5.5.4. Study Observation & Response Criteria

The following is a capsule summary of these response criteria. Please see Therasse et al. for full description [85].

5.5.4.1. Measurability

Measurable disease: require such features so as to be accurately measurable (+/- 10%) in at least one dimension on CT (</= 1.0 cm cuts), MRI, plain X-ray, or medical photographs AND have a major axis of 2.0 cm or more. Tumor lesions seen on images obtained by spiral CT must be 1.0 cm or greater. Ultrasound imaging will be permitted only for superficial lesions. Bone lesions will not be considered under these criteria.

Non-measurable disease: includes bone lesions, effusions, poorly-demarcated pulmonary infiltrates, and lesions <1.0 cm by radiological imaging.

Objective status at examination: Target lesions are to be defined as measurable lesions, up to 5 sites per patient and no more than 2 sites in any one organ.

1. Measurements of target lesions must be provided at evaluations pre-treatment, at 2-3 months, and at 3 month intervals throughout treatment. Nothing in this protocol precludes additional imaging, not explicitly scheduled, via CT, MRI, ultrasound, PET or other modalities if the clinical judgement of the treating physician indicates such would provide significant insight to more accurately aid evaluating CR or PR status.

2. Development of new lesions must be documented.

5.5.4.2. Responses

Responses are to be defined according to the RECIST/iRECIST criteria [78]

5.5.4.3. Toxicity and Evaluation for Adverse Events

Subjects will be queried at each visit regarding:

1. Local reactions to SV-BR-1-GM injections and skin tests.
2. Allergic symptoms such as rhinitis, skin rash, or itching.
3. Performance status, ECOG scale.
4. Inter-current infections
5. Changes in medications (especially pain medications)
6. Subjective sense of well-being or lack thereof
7. Review of systems

Safety/Tolerability responses will be evaluated. Toxicity responses will be characterized and graded according to the new NIH Common Toxicity Criteria, CTCAE Version 4.03 which may be downloaded at http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Unexpected or early death or life-threatening toxicity (such as myocardial infarction, renal failure or thrombo-embolic disease) will be reported immediately to the sponsor, the Institutional Review Board, and to the FDA. The Study site will be responsible for notifying the Sponsor and the IRB. The Sponsor, or their designate, will be responsible for notifying regulatory authorities.

Grade IV toxicity at least possibly related to the experimental therapy will terminate patient accrual until additional review and approval by the IRB and FDA of any necessary changes in the protocol may be indicated.

Grade III toxicity at least possibly related to the experimental therapy will terminate further inoculations in that patient.

A recent publication [61] has summarized the experience with other GM-CSF secreting tumor targeted immunotherapies. In over 450 inoculations, severe toxicity was rare and no treatment-related deaths were described. The most serious toxicities were local allergic/inflammatory responses which were manageable by usual clinical measures.

Adverse events will be responded to and recorded according to section 4.3.

5.5.5. Study Visits

Subjects will be asked to return to the principal investigator's office according to the visit schedule in section 3.3 (Table 2 "Study Calendar").

Because immunological therapies may sometimes require a lengthy time interval to observe response, our concept emphasizes observation over a period of several months. The key evaluation is that which occurs two weeks after the last SV-BR-1-GM in the initial treatment phase. This evaluation, which occurs at month 3, is to identify if there is progressive tumor growth refractory to current treatment. Patients will continue 6 months of treatment, the decision to cease or continue treatment occurs after the 6-month re-evaluation.

Measurable lesions (together with immunological indices) will be evaluated after about 3 months from initiation of therapy and every 3 months of treatment. Performance status and quality of life will be documented regularly using the ECOG/WHO performance scale and the widely used, validated [74] SF-36 questionnaire.

For a list of potential procedures to be performed, see the Procedure and Form Itemization in section 8.

The final visit will be the off-treatment visit, (at the conclusion of approximately 6-12 months of experimental treatment or whenever the patient comes off study).

5.6. STUDY VISITS & PROCEDURES

For a detailed itemization of study visits and procedures, see section 8, “Procedure Itemization”

5.7. DATA COLLECTION

Relevant study data will be collected on each subject and entered into an Electronic Data Capture (EDC) system. The URL for the EDC system is https://login.medrio.com. Supported operating systems are Microsoft Windows XP, Microsoft Windows 2000, Microsoft Windows 7 and 8, Microsoft Vista, and Mac OS X. Microsoft Internet Explorer (version 9 and later), Firefox (version 27 and later), Chrome (version 30 and later), and Safari (version 9.0 and later) are acceptable web browsers.

Medrio software supports compliance with regulations such as 21 CFR Part 11, Annex 11, EU Safe Harbor, Good Clinical Practice, and HIPAA. Procedural controls include electronic audit trails of all changes to study data, electronic signatures, data encryption, and access restrictions to Protected Health Information (PHI). Access to the Medrio EDC system will only be granted to study personnel after training is conducted. User accounts are permission based which grants limited access and functionalities dependent upon permissions granted by study administrator. All data that goes into and out of the server is encrypted using 128-bit Secure Sockets Layer (SSL) and 1024-bit RSA public keys. The servers, hosted by Medrio, are housed in a fully redundant N+1 data center with redundant power, cooling, and network connectivity. All servers reside behind Cisco firewalls and advanced intrusion detection/prevention systems. Medrio performs nightly backups to locations both on-site and off-site and maintains redundant hardware.
Data collection will begin at the signing of informed consent. All data must be submitted within 72 working hours of the visit in which data was collected. Edit checks (often called queries)

will fire in real time as data is being entered to ensure quality data is provided. In addition to edit checks, manual queries will be generated by Data Managers and Monitors. Sites will have 10 working days to address all edit checks and manually created queries. Source Data Verification (SDV), Data Management Review and electronic signature by site PI will all take place prior to locking data.

5.8. CONFIDENTIALITY& RECORDS

5.8.1. General Precautions

The confidentiality of subjects will be protected. Names and other identifying information will not appear on any study forms, except the Informed Consent, HIPAA Authorization and the Enrollment Log, where subject names will be matched to their unique Study Number.

Subsequent study forms and any laboratory tests will be identified only by a unique Study Number assigned to each subject, which is recorded on the EDC (see section 9.1.6).

The source documents (which meet the record-keeping requirements of §312) are maintained and protected in a fireproof file cabinet in a locked room. Written research records will be kept in a locked room, in a locked file cabinet accessible only to the principal investigator and only those members of staff with specific project responsibilities. Research charts will not be labeled by patient name but rather by unique identification code. Records will be maintained for at least 7 years after completion of the drug investigation.

Research data will be stored and analyzed by computer. The research team members will be the only people to have access to the computer file, which is protected with a confidential password. Computer records are not totally immune to review by unauthorized persons, (hackers), but will be protected by password and unique ID of each patient.

Research records may be also be reviewed by government organizations such as the Food and Drug Administration, the Institutional Review Board, and other persons who are required to watch over the safety and effectiveness of medical products and therapies or the conduct of research. If the research record is reviewed by any of these groups, there may be a need to examine the entire medical record and/or hospital charts. Under certain circumstances, Congress or a court order could obtain research records. While every effort will be taken to keep information confidential, under special circumstances, this could mean public disclosure.

5.8.2. Study Information Leaving the Offices of the Investigator

All identifying information will be stripped from study records provided to the Study Monitor. Data on a subject generated by other physicians and by the Principal Investigator will be provided to the Study Monitor only after being de-identified. No consent forms or other documents identifying the subjects in any way will be provided to the Study Monitor, except to be provided at the site during a monitoring visit. The Study Monitor will have access to all study records to verify proper conduct of the study.

5.9. COMPENSATION

Subjects will not be paid for their participation. Compensation for travel or other expenses associated with study procedures require pre-approval from the Sponsor. Patients (or their insurance, e.g. Medicare) are expected to be responsible for all usual and customary fees associated with office visits, study tests and procedures, and follow-up costs, as is customary for national cancer trials.
There will be no fee attached to the preparation or quality control testing of the SV-BR-1-GM, but standard fees for doctor visits and nurse visits will apply.

5.10. SPECIMEN LABELING INFORMATION

Laboratory specimens and test results will be coded only with a unique identifying number (i.e. "Study Number"), date of collection, and the protocol number. The Consent Forms and Enrollment Log will be the only places on which subject names will be linked to their Study Number. (Names and other identifying information of screening failures will not be recorded.). Biological specimens will be stored according to the sponsor's laboratory SOPs, and used for ongoing research only as specified in the supplemental enrollment form, "Consent for the Use of Blood or Tissue." (See section 9)

6. MONITORING PROCEDURES

6.1. GENERAL PROCEDURES

On-site study monitoring will be performed in accordance with 21 C.F.R. §312.60 obligations. The Study Monitor will perform in accordance with 21 C.F.R. §312.50.

Study monitors will visit the site to:

- Verify compliance with human subjects and other applicable research regulatory guidelines and requirements.
- Assess adherence to the study protocol, study specific procedures and Standard Operating Procedures.
- Confirm the quality and accuracy of trial conduct, recording and reporting by clinical site.

Site investigators will allow study monitor to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, electronic case report forms), as well as observe the performance of study procedures. Investigators will allow inspection of all study-related documentation by sponsor's and regulatory authorized representatives. A site visit log will be maintained at the study site to document all visits.

Any amendments, revisions, or updates to the research activities will be submitted to the IRB and FDA, in accordance with 21 C.F.R. §312.30, §312.66, and §50.27. Such modifications may include, but not limited to, changes to the protocol, informed consent documents, investigators, sources of funding, etc. A change may be implemented prior to approval by the IRB or FDA only when it is necessary to eliminate apparent immediate hazards to the research subjects in accordance with 21 C.F.R. §312.66. In such an instance, the IRB (21 CFR 312.53.c.1.vii) and FDA will be notified 5-10 days following its implementation.

6.1.1. Data Monitoring and Auditing of Data

The monitors and study coordinator will verify accuracy of data, regularly review source documents and compare these to ongoing study data input. Data collecting and reporting will proceed in accordance with the protocol. All data correction notes are corrected within the eCRF. This procedure maintains the original record and identifies the dates of correction. Individual making the correction sign and date, and give the reason for any changes. The data monitors review the eCRFs weekly and query the investigational sites for missing or incomplete data. The site visit monitor will compare source documents to the eCRF to verify for completeness and accuracy.
All eCRF documents, forms, lab results, hospital records, x-rays, billings, etc. will be reviewed and used as comparison, to verify the accuracy of the electronic case report forms.

6.2. AFTER COMPLETION OF THE STUDY

The conduct of the study termination or “End of Study Visit” will follow all GCPs and FDA guidelines. The monitor will conduct the study termination visit to:

1. Review all regulatory files for completeness;
2. Compete the verification of all data in eCRFs with source documentation;
3. Ensure that any equipment on loan is returned;
4. Meet with the research team to discuss the results of:
   - The final audit of the regulatory files,
   - The final source data verification,
   - The possibility of a quality assurance and /or FDA audit,
   - The requirement for data storage.

The study monitor will discuss with the principal investigator regarding any follow up for serious adverse events after formal termination from study.

At the completion of the investigators' participation, a final report will be reviewed by the monitors and submitted to the FDA, in compliance with 21 CFR 312.64(c) within two weeks. To ensure timely preparation and delivery of this document, time and resources will be allocated to complete the final document as part of the budget and planned timeline.

The study monitor will discuss with the principal investigator the next phase of the trial, the possibility of future studies, etc. and will ensure that:

1. All study drug is accounted for
2. Any study materials not used for this study are returned or destroyed
3. Study files are prepared for long-term storage

7. STATISTICAL CONSIDERATIONS

The primary endpoint is safety, which does not require statistical analysis, nor does the decision to expand the patient cohort from 10 subjects to 25-40. Subjects who do not reach the first post-dose tumor assessments may be replaced at the discretion of the Sponsor. However, for scientific data review, de-identified data will be entered onto CRFs and from there into a computer database for possible statistical analysis.

In addition to those variables specifically mentioned in this protocol, which are related to the current treatment and assessments, information on a variety of patient characteristics will also be entered, including but not limited to demographics (age, sex, race/ethnicity), medical history (stage at diagnosis, ER/PR/HER2neu, genomic analysis per community practice, prior cancer treatments, time from diagnosis to first metastases, sites of disease, etc.), physical exam characteristics, and date of death for computing survival time from first SV-BR-1-GM inoculation.

7.1. DATA of SPECIAL INTEREST

In addition to the above expected demographic variables and endpoints, several other characteristics will be addressed, including:

1. Changes in weight, performance status, pain;
2. Quality of life (as measured by the SF-36);
3. Delayed type hypersensitivity to SV-BR-1 or SV-BR-1-GM and to recall antigens;
4. Immunological responses (if feasible, to perform in real time);
5. CEA, CA 27.29 (or CA 15-3 if preferred by the Investigator)

The HLA phenotype will be tested before beginning the program, as many consider the presence of HLA A2 a necessary condition for developing an immune response to peptide antigens displayed to the T-cell receptor. This locus is present in about 45% of patients, about 10% higher in Chinese and about 15% lower in African-Americans. The absence of HLA-A2 has not been an exclusion criterion for our previous work, but given its frequency, data gathering seems warranted as it may show some correlation. While not present on SV-BR-1-GM it was present on the patient described in our case report [19]. Of 8 HLA alleles phenotypically identified on SV-BR-1, 5 were held in common with this responder case (2 of which, HLA-A*11:01 and HLA-DRB3*02:02, were recently confirmed at the allele level; presented at the annual American Association for Cancer Research meeting, 2016, New Orleans); the significance of this is not known but subject to further study. HLA data will be accessible only to the medical monitor and BriaCell personnel; no HLA data is to be released to any investigator or associated staff.

7.2. REVIEW of STUDY DESIGN

This is a phase I/IIa safety analysis. The initial 10 patients will be enrolled, which will trigger a pure safety analysis of the treatment. Once deemed safe an additional 15-30 patients will be enrolled to complete the primary, secondary and exploratory end points.

7.3. RESPONSE DEFINITIONS

Both objective tumor response (CR or PR) and immunological response will be considered as evidence of activity. Criteria for clinical response have been described in detail in the discussion of RECIST and iRECIST. Three tests will be used for evaluation of SV-BR-1-specific immunological response. Serum antibody levels against live SV-BR-1 cells will be measured by cell suspension ELISA. T-cell mediated response will be measured by delayed type hypersensitivity (DTH) skin test and by flow cytometry. The latter test is designed to calculate the frequency of peripheral blood T cells producing interferon-gamma in response to stimulation with monocytes pulsed with SV-BR-1 cell lysate. For cell suspension ELISA and flow cytometry assay, a 1.5-fold increase from pre-SV-BR-1-GM to post-SV-BR-1-GM level is considered evidence of response [87]. For DTH, an induration of >5mm in diameter is commonly considered evidence of reaction [83], although erythema has been considered informative in one recent report [88]. If a patient has either a clinical response or an immunological response on any of the three measures, he/she will be considered to have a biological response. In addition, data may later be analyzed using the recently published iRECIST criteria [89].

These criteria for response (as well as an alpha error rate of 0.10) are being used because this is an early trial of a new regimen that is expected to be well tolerated and is being used in patients who have failed the standard therapeutic approaches. Their survival time is expected to be limited under any circumstances, and it is important not to miss a possibly active treatment regimen. Insofar as the patients for this regimen will have very advanced cancer, the absence of toxicity will be considered very significant and will encourage consultation with the FDA for advice for planning further investigations in patients with more favorable prognoses and more robust immune capabilities.

Also, early termination can occur based on toxicity, as described earlier in the toxicity section.

7.4. DATA ANALYSIS

A variety of statistical analyses will be performed to assess the relationship between clinical response, immunological response, and possible prognostic factors. The appropriate statistical test will be determined by the bio-statistician.

Multiple regression and/or Cox regression will be performed to identify factors predictive of response if the number of subjects entered into the study so permits. This may include logistic regression when using response as the endpoint and Cox regression when using survival time. Other parametric and nonparametric tests will be used as appropriate to evaluate relationships of interest. For all tests, criterion for statistical significance will be set at $p < 0.05$, two-tailed test.

The principal investigator will review clinical and laboratory data at the times of reimaging and restaging or earlier as needed. Protocol deviations will be entered onto a form to be included in the regulatory binder. Missing data, patient absence or other non-compliance will be documented in a Note to File, copied to the IRB, and included in the annual report unless safety concerns warrant prompt FDA filing as per the criteria for Serious Adverse Events.

8. PROCEDURE AND FORM ITEMIZATION

Cycle I

Day	Procedure
Within 2-4 weeks before starting Initial Treatment Phase (ITP)	Get blood tests and imaging tests. HLA profile if not done already; Serologic Markers; Urinalysis. Blood /specimens for research. Baseline physical and medical history. Decision about eligibility. SF-36 "Quality of Life" form. Explanation of program, questions answered, study enrollment forms reviewed and signed. (Section 9 for forms) Cardiac assessments: baseline ECG, cardiac troponin (cTn), NT-proBNP and an estimation of left ventricular ejection fraction (LVEF) by either cardiac echo or MUGA scan.
2-3 days before starting ITP	Get routine blood tests. Serologic Markers; Urinalysis. Blood/specimens for research. Abbreviated physical exam (only if not performed within the past 2 weeks). Beta-HCG serum pregnancy test for women of childbearing potential within 7 days of first SV-BR-1-GM. SF-36 "Quality of Life" form. Have low-dose cyclophosphamide (Cytoxan) premedication (to possibly enhance immune response).
Day 0	**Start of Initial Treatment Phase (ITP)** Anergy test. (to occur with cycles 1, 3, 6, 9, 12) Have DTH (~10^6 BriaTest™ or SV-BR-1-GM) and anergy (Candin) skin test injections in forearm. Evaluate for immediate hypersensitivity to BriaTest™ or SV-BR-1-GM. Receive injections of full dose SV-BR-1-GM into skin of right and left thighs and two places on upper back (unless allergy to skin test is seen).
Day 2 & 4 (±1)	Evaluation of skin tests (anergy to Candin and DTH to BriaTest™ or SV-BR-1-GM) and of SV-BR-1-GM injection sites. Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on day 2 (± 1 day) and 4 (± 1 day) to possibly enhance immune response.

Cycle 2

Day	Procedures
Day 11 or 12	Brief physical and update of medical history.

	Get routine blood tests. SF-36 "Quality of Life" form. Low-dose cyclophosphamide (Cytoxan)
Day 14	Have DTH (~10^6 BriaTest™ or SV-BR-1-GM) skin test injections in forearm. Evaluate for immediate hypersensitivity. Any evidence of immediate hypersensitivity precludes dosing with SV-BR-1-GM. Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Day 16 & 18 (±1)	Evaluation of skin tests (DTH to BriaTest™ or SV-BR-1-GM). Evaluation of SV-BR-1-GM injection sites. Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM to possibly enhance immune response.

Cycle 3

Day	Procedures
Day 25 or 26	Brief physical and update of medical history. Get routine blood tests. SF-36 "Quality of Life" form. Low-dose cyclophosphamide (Cytoxan).
Day 28	Have DTH (~10^6 BriaTest™ or SV-BR-1-GM) and anergy (Candin) skin test injections in forearm. Evaluate for immediate hypersensitivity to BriaTest™ or SV-BR-1-GM. Any evidence of immediate hypersensitivity to BriaTest™ or SV-BR-1-GM precludes dosing with full dose SV-BR-1-GM. Anergy test (Candin) is to occur with cycles 1, 3, 6, 9, and 12. Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Day 30 & 32 (±1)	Evaluation skin tests (anergy to Candin and DTH to BriaTest™ or SV-BR-1-GM) and of SV-BR-1-GM injection sites Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM to possibly enhance immune response.

Cycle 4

Day	Procedures
Day 53 or 54	Brief physical and update of medical history. Get routine blood tests. SF-36 "Quality of Life" form. Low-dose cyclophosphamide (Cytoxan).
Day 56	Have DTH (~10^6 BriaTest™ or SV-BR-1-GM) skin test injections in forearm. Evaluate for immediate hypersensitivity. Any evidence of immediate hypersensitivity precludes dosing with full dose SV-BR-1-GM.

	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Day 58 & 60 (±1)	Evaluation of skin tests (DTH to BriaTest™ or SV-BR-1-GM). Evaluation of SV-BR-1-GM injection sites. Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM to possibly enhance immune response.

Cycle 5

Day	Procedures
Day 81 or 82	Brief physical and update of medical history. Get routine blood tests SF-36 "Quality of Life" form. Low-dose cyclophosphamide (Cytoxan).
Day 84	Have DTH (~10^6 BriaTest™ or SV-BR-1-GM) skin test injections in forearm. Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on upper back.
Day 86 & 88 (±1)	Evaluation of skin tests (DTH to BriaTest™ or SV-BR-1-GM). Evaluation of SV-BR-1-GM injection sites. Evaluate for immediate hypersensitivity. Any evidence of immediate hypersensitivity precludes dosing with SV-BR-1-GM. Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM to possibly enhance immune response.

Clinical Evaluation Visit

Day	Procedures
Day 110 (approx.)	Get routine blood tests and imaging tests. Serologic Markers; Urinalysis. Blood and urine for research. Physical exam and update of medical history. SF-36 "Quality of Life" form. Cardiac assessments: An ECG and estimate of LVEF (by the same method) will be performed after 3, 6 and 12 months on study if the subject remains asymptomatic, or earlier if a patient becomes symptomatic.

Cycle 6, 7, 8 - Refer to procedure as cycle 3, 4 and 5.

Re-Evaluation Visit - Refer to procedure for Clinical Evaluation Visit. If patient has a non-progressive response and desires to continue treatment, may proceed for 3 additional cycles with re-evaluation after the 3 cycles. If patient progresses or choses to stop treatment they will be considered off-treatment.

Optional Cycle 9, 10, 11 - Refer to procedure as cycle 3, 4 and 5.

Re-Evaluation Visit - Refer to procedure for Clinical Evaluation Visit. If patient has a non-progressive response and desires to continue treatment, may proceed for 3 additional cycles with re-evaluation after the 3 cycles. If patient progresses or choses to stop treatment they will be considered off-treatment.

Optional Cycle 12, 13, 14 - Refer to procedure as cycle 3, 4 and 5.

Off-Treatment Visit

Day	Procedures
Day will vary	Get routine blood tests and imaging tests. Serologic Markers, Urinalysis. Blood and for research. Physical exam and update of medical history. SF-36 "Quality of Life" form.

Flexibility within cycles
-Pretreatment: IV low-dose cyclophosphamide (300 mg/m^2 or a lower dose with the Sponsor's approval) C 2-3 days before SV-BR-1-GM inoculation
-Treatment: intradermal injection of SV-BR-1-GM (5-50 x 10^6 cells) in 4 divided doses into the upper back and upper thighs
-Posttreatment: intradermal Interferon-alpha-2b (Merck) alpha (10,000 U) into each SV-BR-1-GM inoculation site at 2 and 4 days ± 1 day.

Flexibility between cycles can be +/- within one week under special circumstances as approved by PI.

9. FORMS AND REFERENCES

9.1. CONSENT, SCREENING & ENROLLMENT FORMS

9.1.1 Primary Informed Consent Form
9.1.1A Attachment - Study Calendar
9.1.2 HIPAA Authorization Form
9.1.3 Consent for Use of Blood or Tissue for Research
9.1.4 Study Information Sheet (FAQs)
9.1.5 Screening Evaluation Form
9.1.6 Screening & Enrollment Log

9.1.1. Primary Consent Form

A Phase I/IIa Study of the SV-BR-1-GM in Metastatic or Locally Recurrent Breast Cancer Patients

Principal Investigator (Study Doctor): [Name of Investigator]

CONSENT TO BE A RESEARCH PARTICIPANT

This is a clinical trial, a type of research study. ***A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.***

Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You don't have to make this decision now. You may also take this consent form and other materials and discuss your decision with your friends and family. You can also discuss it with your own doctor, and health care team. If you have any questions, you can always ask the study doctor or their designate for more explanation.

You are being asked to consider taking part in this study because you have recurrent breast cancer that has not responded to traditional treatments.

Why is this study being done?

The purpose of this research program is to study the safety and effectiveness of an experimental immunotherapy for advanced cancer. In this study, we want to see whether SV-BR-1-GM injections help boost your immune system and/or help control or help improve your cancer. The researchers will also be studying the safety of SV-BR-1-GM to investigate what effects good and/or bad the injections have on you and your cancer. Initially, ten patients will take part in the study. If there are no serious side effects, an additional 15 patients may be treated to evaluate the same effects.

What is the experimental therapy?

The therapy is called SV-BR-1-GM. This is created with a human breast cancer cell line that has been genetically engineered to produce a substance called "GM-CSF," which occurs naturally in the body. We would like to see if injecting the investigational agent into your body in combination with other drugs will have an effect on your cancer. Before injection the tumor cells in the SV-BR-1-GM are given a treatment similar to x-ray therapy so they do not spread or grow.

SV-BR-1-GM has been under study for many years, to bring it to this stage for evaluation in additional research participants. The prior results in this program have shown some preliminary effect on their brain tumor metastases in the one patient affected. The intended study will further explore the activity of the product.

What is required to be part of this study?

To fully consider whether you want to take part in this study, you will be asked to read many forms, and sign them if you choose to take part. These include:

1. This consent form.
2. A separate consent form for future use of your blood and/or tissue samples.
3. An information sheet with frequently asked questions about this type of research.

After considering all the information carefully, and if you choose to take part in this study, you will first be evaluated for qualifying medical conditions.

To be considered eligible for the study, you will need to have the following conditions:

- You must have a qualifying type of stage four (Stage IV) breast.
- You must also have evidence that surgery, radiation, or other medical therapies have not helped you.
- You must have received chemotherapy (and/or hormonal therapy, if appropriate) in the past.
- You must be expected to live for at least another 4 months.
- You must be in charge of your own health care decisions.
- You must have acceptable blood and other test results that will be done to see if you are eligible.

You may not participate in this study if any of the following apply:

- You are not eligible if you are a woman who is pregnant or nursing.
- If you are a woman of childbearing age, you must also be careful not to BECOME pregnant or nurse a child while you are in this study because the researchers don't know how the SV-BR-1-GM may affect a developing baby. If you are a woman of potential childbearing age, you must have a negative pregnancy test within 7 days before starting this study. You must then take appropriate measures to keep from becoming pregnant. If you become pregnant during the study, you should report this to the study doctor or their designate.
- If you have recently had chemotherapy, hormonal therapy, XRT, Immunotherapy, or general anesthesia/major surgery, you must have complete recovery from expected side effects of the last treatment (usually a period of 3 weeks).
- If you have another cancer in any other part of your body, other than the primary breast, you usually will not qualify. However, you may still take part in the study if the other cancer has not needed treatment in the past 24 months.
- If you have cancer spread to the brain, you understand that it will be necessary to monitor the tumor with MRI imaging about every 3-4 weeks. You understand that the standard of practice in the community is to initiate radiation therapy and that delaying radiation therapy to see SV-BR-1-GM effect is experimental.
- You must not be taking Coumadin or similar anti-clotting medicine, or systemic steroids (at a dose greater than 10 mg a day of prednisone), or "beta-blockers" (a blood pressure medicine).

- You must not have certain rheumatologic (Lupus), psychiatric (unpredictable to major psychosis), immune disorder (such as HIV or AIDS), or any other major medical problems.

If you decide to take part, the Study Doctor or their designate will discuss with you your complete health history (and social history as it relates to your health).

What will be done to see if I am eligible?
There will be many tests to see if you are eligible, and to provide data that can be compared at the end of the study to see how SV-BR-1-GM worked. Because there are so many tests, and the timing of when these tests is important, it might take several visits to this office to get them all done in the order required for this study.

I. Procedures that will be done at the treatment office. (Most of these will be done today if you agree to take part and sign the consent forms):

1. Questions about your medical & social history (screening only).
2. A complete physical exam, including vital signs.
3. About 40 ml of blood will be collected from your arm using a needle and small tubes for future research purpose, and other blood tests will be done in about 14 days of receiving the first SV-BR-1-GM injection.
   a. Tests will be done including CBC, differential, platelets, T and B subsets, comprehensive metabolic biochemical profile, LDH, GGT, uric acid, HLA profile. (The study doctor or their designate will explain to you what all these tests mean).
   b. Cancer blood tests will also be done, for example, CEA and CA 27.29 (or CA 15-3) serology.

4. For women of childbearing potential, a pregnancy test will also be done from the same blood samples in about 7 days before receiving the first SV-BR-1-GM injection.

5. This office will collect urine for a routine urine test and for possible future research.

6. You will be asked to fill out a questionnaire that gathers information about your quality of life.

7. Tests will also be done to see if you are allergic to SV-BR-1-GM or its ingredients. These tests, called “immunohistological” or “anergy” tests, will be done by using a needle to inject a small amount of BriaTest™ (which is closely related to SV-BR-1-GM) or SV-BR-1-GM just under the skin of your forearm, and observing the results over several days.

8. A buccal swab (getting cells from inside your cheek with a Q-tip) will be collected to perform HLA typing (similar to tissue typing for transplantation). This is a genetic test.

II. Procedures that need to be scheduled (within 28 days of receiving the first SV-BR-1-GM injection):

1. A regular chest X-ray (if determined necessary by your study doctor).
2. A CT scan of your chest, abdomen, and hips (or PET scan at the discretion of your study doctor).

3. A bone scan, and/or selected bone X-rays if there is any clinical suspicion of bone cancer.
4. A breast MRI or mammogram may done. Also, a PET test may be required. If you have already had these done you may be asked to share the results with the study doctor or their designate.
5. A brain scan (MRI or CT technique) will be done if you have any neurological symptoms related to your cancer.
6. An electrocardiogram.
7. An evaluation of heart function either by a cardiac echo or a radioactive tracer scan.

When all your eligibility tests have been done, the study doctor or their designate will make a decision about whether you can take part in the study. You will be notified by the office of test results and final decision of the study doctor. If any test results show anything that could affect your health, or might need further testing for your medical care, your own doctor(s) will be notified. You will be asked to sign a release form for this purpose.

What will happen when I receive the SV-BR-1-GM?
Receiving the experimental therapy is a detailed process that happens in a "cycle". Each cycle spans 7 to 9 days, and requires 4 different visits to this office; each about 2 days apart. There will be 15 cycles of receiving SV-BR-1-GM over the course of 13 months during the treatment phase of this study. A schedule of the cycles is attached to this consent form for your reference.

<u>During each cycle, the following procedures will be done</u>:

<u>Visit 1</u>: 2 days before receiving the SV-BR-1-GM, you will first have lab tests done. You will then receive a medicine to prepare your immune system. This medicine is called cyclophosphamide (Cytoxan). It is widely used in doses that are 2-3 times more than that used in this study. This drug will be injected into a vein (i.e. given intravenously) over the course of about 60 minutes. You will also receive a drug to reduce nausea.

Starting with the 2nd SV-BR-1-GM cycle, other procedures will be done at this first visit of each cycle, including a brief physical exam and update of your medical history. You will also be asked to fill out the quality of life questionnaire again. This visit will take about an hour.

<u>Visit 2</u>: In a separate office visit 2-3 days later, you will first have the allergy test injections done on your forearm. After 20 minutes, if all is well, you will receive injections of the experimental therapy, SV-BR-1-GM. In this study, the SV-BR-1-GM is injected into four places (two sites: on the upper back and two thighs, right and left). After the injections, you will be asked to remain in the office for 60 minutes to see if there are any side effects. This entire visit will take about 90 minutes.

<u>Visit 3</u>: 1-3 days after you receive the SV-BR-1-GM, you will return to this office to receive a drug called "Interferon-alpha". Interferon-alpha-2b (Merck) is available from drug companies and is also widely studied to improve immune function. At this visit, a very small amount of Interferon-alpha-2b (Merck) will be injected into same places as the SV-BR-1-GM, to help boost the local immune reaction.

Visit 4: In another office visit 1-3 days later (3-5 days after SV-BR-1-GM), Interferon-alpha-2b (Merck) injection will be repeated again. Each of these visits will take only about 15 minutes. During the first month of the study, you will be asked to come in to this office for 3 SV-BR-1-GM cycles, totaling 12 visits. This is an important time commitment on your part, and you should consider the impact it will have on your schedule.

Evaluation Periods

After the first 3 cycles, you will start monthly cycles for a total of 8 cycles over 6 months. After 4 or 5 cycles (2-3 months) blood and imaging tests will be done, so that the results can be compared to baseline. After 8 cycles (6 months) blood and imaging tests will be done, to evaluate the results over time. Some extra blood will be drawn at some visits to measure cancer cells that may be in your blood. The study doctor or their designate will explain exactly which tests will need to be done in your case. Based on the results of the 6 month tests, you and your doctor will make a decision whether you are eligible to proceed for the optional 3 months of treatment (3 more cycles). If you are eligible and chose to proceed with the optional treatments, another re-evaluation of imaging and labs will be performed after cycle 11 (month 9). If you are still eligible (based on the 9 month tests) for continued optional treatments and you chose to proceed you will have a total of 12 months of treatment and 14 cycles of treatment. Imaging tests may be performed more frequently if your doctor thinks this is advisable. The electrocardiogram and the evaluation of heart function will be repeated after 3, 6 and 12 months or more frequently if you develop symptoms like chest pain, shortness of breath or weakness.

Monthly Maintenance Cycles

After the first month, if you continue in the study, you may be scheduled to complete 5 additional SV-BR-1-GM cycles, each about a month apart. There will be one SV-BR-1-GM cycle each month, with the similar visits, timing, and procedures described above. After each 3 SV-BR-1-GM cycles (about 3 months apart), there will be another Evaluation Period to see if you should continue on the study. This will involve the similar tests and evaluations described above.

After the last SV-BR-1-GM treatment (about 6-12 months into the study), you will again have blood and imaging tests for a final comparison. You will not participate in more than 14 SV-BR-1-GM cycles during the entire study. The total length of your participation in the "treatment phase" of this study depends on many scheduling factors, but is expected to last about 6-12 months.

Should your doctors decide that SV-BR-1-GM is not helping, you will be taken off protocol. You will not be able to receive further SV-BR-1-GM and you may receive whatever treatments that are recommended by your doctor.

The attached Study Calendar details the timing of all these visits, procedures, and follow-up. You will be asked to stick with this study schedule as closely as possible, and to tell the study doctors or their designate about any good or bad changes to your health.

What happens after the study ends?

Two weeks after you are finished with the last SV-BR-1-GM cycle, the study doctor or their designate will ask you to visit the office for follow-up blood and imaging tests, and a final physical exam.

If you are not coming to our office for other reasons, we would like to call you, your doctor, or the person you may choose, on the telephone every 6 months to see how you are doing. This will help us look at the long-term effects of the SV-BR-1-GM.

We would like to keep track of your medical condition for the rest of your life. (You can decide to stop the phone calls at any time.) A special form is on hand ("Designation of Proxy") for you to provide us with the contact people you wish to designate.
The results of the study may be published in medical journals or other media. Your identity will not be disclosed in any of the publications, presentations, or articles that result from this study.

Can I stop being in the study?
Yes. You can decide to stop at any time. Simply tell the study doctor or their designate if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the SV-BR-1-GM can be evaluated for your safety. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you, and what information (if any) you would like to share with your other doctors.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped for any reason.

RISKS AND BENFITS OF BEING IN THIS STUDY

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects, as part of your regular medical care outside of the study. Many side effects go away soon after you stop taking the SV-BR-1-GM. In some cases, side effects such as allergic reactions could be serious long-lasting, or even produce risk of death. One patient on this study died. She was a 54-year-old woman with breast cancer which had spread throughout one breast and the outside of the lungs. In her second cycle of treatment, she received the cyclophosphamide and came in 2 days later feeling weak and short of breath. She received the SV-BR-1-GM and was sent to the emergency room for the shortness of breath. Her heart stopped and attempts to revive her were not successful. No autopsy was performed. The Investigator thought this death was unlikely related to SV-BR-1-GM.

You should always notify your study doctor right away of any side effects that you have while taking part in the study.

Risks and side effects related to ***the experimental treatment*** include:

Likely

- Pain from injection
- Redness, swelling, itch developing at the injection sites

Less likely

- Flu-like symptoms such as fever, chills, aches, tiredness
- Rash and/or itch on body, away from injection

Rare but serious

- Wheezing, hives (allergic reaction), which could be recurrent in the future.
- Food allergy to beef or yeast products such as bread, pasta (transient)

Risks and side effects related to ***low-dose cyclophosphamide (Cytoxan)*** include:

- Nausea (manageable with medication)
- Lack of appetite, and less commonly vomiting, and a decrease in blood counts

Risks and side effects related to the ***low-dose Interferon-alpha-2b (Merck)*** include:

- Local pain
- Redness, swelling, itch
- Flu-like symptoms

Risks and side effects related to ***skin tests*** include:

- Pain
- Allergy
- Redness, swelling

For more information about risks and side effects of the study treatment and drugs, ask your study doctor.

Are there other non-medical risks if I take part in the study?

Yes. You have already been provided with papers describing our office privacy precautions, and although we will try our best, we cannot guarantee total privacy. We will do all we can to make sure that the personal information in your research records will be kept private. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, or in the media your name and other personal information will not be used.

Organizations that may look at and/or copy your research records for quality assurance, and data analysis include:

- The Institutional Review Board (a group that watches the study to protect you and your rights)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA)

As you take part in the study, you may require travel, finding accommodations, and restaurants if you do not live nearby. SV-BR-1-GM cannot be mailed or transported to your community

physician. These arrangements will be your own financial responsibility, and there may be risks involved.

Another risk is that you will not be allowed to receive other chemotherapy during the study and participating in this study could possibly disqualify you from entering future research studies. Although SV-BR-1-GM is considered safe, regulatory bodies may be interested in carrying out autopsy, at the time of death of the patient. You and/or your family are under no obligation to approve an autopsy. If there are personal, religious, or any other objections, it is your right not to give permission.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. While doctors hope SV-BR-1-GM will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these therapies as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Getting no treatment.
- Getting comfort care also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

What are the costs of taking part in this study?
There is no fee for the SV-BR-1-GM, but your study doctor, the laboratories, and imaging centers performing study procedures and tests will require payment for goods and services (for example, office visits, medicines such as cyclophosphamide, and Interferon-alpha-2b (Merck), IV tubing and syringes used for injections, etc.) according to customary fee schedules.

You and/or your health plan or insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in research studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid or compensated in any way for taking part in this study. Travel, lodging and other reasonable expenses may be reimbursed by the Sponsor when requested by the Investigator but must be pre-approved by the Sponsor.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site www.cancer.gov

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237)

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor if you feel that you are having a side effect or have been injured because of taking part in this study. You can tell him in person or call him/her. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. No arrangements have been made, or funds set aside, for the treatment of injuries resulting from taking part in this study.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution, or any other of your choice.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form. Any questions regarding rights as a patient may be referred to the Institutional Review Board at: Western IRB (1-800- 562- 4789).

Who can answer my questions about the study?
You can contact your study doctor about any questions or concerns you have about this study. If there are any questions or concerns that you don't feel comfortable discussing with him, you can ask the sponsor, your own doctors, trusted persons, or the Institutional Review Board listed above.

Please note: There will be several other forms given to you about this study, including one that informs you about research studies that could be done with biological specimens collected from people who are taking part in the main study. You can give permission for your biological specimens to be used in these additional studies if you want to, or you can refuse. You may withdraw your specimens from further study at any time if you change your mind. You can still be a part of the main study even if you say 'no' to take part in any of these additional studies.

Where can I get more information?
The study doctor is available to answer questions:
[Name of Investigator]
Phone: (XXX) XXX-XXXX.

You may call the National Cancer Institute's Cancer Information Service at:

- 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/

- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

SIGNATURES

Participant: I have been told about this study and have taken time to ask questions and think about my decision. I agree to participate.	**Person obtaining consent**: I have talked with the participant about the study and answered all of his/her questions. I accept his/her consent.

Printed Names

Signatures

Date / Time

Study Number: _____.

9.1.1(A) – Study Calendar (Attachment to the Consent Form)

STUDY CALENDAR

Screening and Eligibility Procedures

Within 2-4 weeks before starting Initial Treatment Phase (ITP)	**FIRST:** Explanation of study, questions answered, enrollment forms reviewed and signed
	Get screening blood tests, heart evaluation and imaging tests. (The study doctor or their designate will help you schedule these.)
	Fill out the "Quality of Life" questionnaire.
	Initial physical and medical history done.
	Decision about eligibility

Initial Treatment Phase (ITP) - Cycle #1

2-3 days before receiving SV-BR-1-GM	Brief physical and update of medical history (only if not performed within the past 2 weeks).
	Get routine, research blood tests and urine tests.
	Fill out the "Quality of Life" questionnaire.
	Receive low-dose cyclophosphamide (Cytoxan) pre-medication to possibly enhance immune response.
Day 1	**Receive first SV-BR-1-GM injections**
	Have Anergy and DTH skin test injections in forearm.
	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back (unless allergy to skin test is seen).
Day 3 (±1) and	Evaluation of skin tests, SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on day 2 (± 1 day) and 4 (± 1 day) to possibly enhance immune response.
Day 5 (±1)	Evaluation of skin tests, SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM.

ITP - Cycle #2

Day 12 or 13	Brief physical and update of medical history.
	Get routine blood tests.
	Fill out the "Quality of Life" questionnaire.
	Receive low-dose cyclophosphamide (Cytoxan) pre-medication.
Day 15	Receive DTH skin test injections in forearm.
	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Day 17 (±1)	Evaluation of skin tests, SV-BR-1-GM injection sites.

	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM.
Day 19 (±1)	Evaluation of skin tests, SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM.

ITP - Cycle #3

Day 26 or 27	Brief physical and update of medical history.
	Get routine blood tests and research tests.
	Fill out the "Quality of Life" questionnaire.
	Receive low-dose cyclophosphamide (Cytoxan).
Day 29	Have Anergy and DTH skin test injections in forearm.
	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Day 31 (±1)	Evaluation of skin tests, SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (±1) and 4 days (±1) after SV-BR-1-GM.
Day 33 (±1)	Evaluation of skin tests, SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (± 1 day) and 4 days (± 1 day) after SV-BR-1-GM.

Monthly Maintenance Phase - Cycles 4 through 8 (1 month apart)

Visit 1	Brief physical and update of medical history.
	Get routine blood tests.
	Fill out the "Quality of Life" questionnaire.
	Receive low-dose cyclophosphamide (Cytoxan).
Visit 2	Have skin test injections in forearm.
	* Cycle # 6 only - Have Anergy test injections.
	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Visit 3,4	Evaluation of SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (±1) and 4 days (±1) after SV-BR-1-GM.

Evaluation Period – Collected After Cycle 4, Before Cycle 6

Approx. 2 wks later	Get routine blood tests, research tests, urinalysis, heart tests and imaging tests; Serologic markers.
	Brief physical and update of medical history.
After every 3 Cycles	Fill out the "Quality of Life" questionnaire.

Repeat Evaluation Period – Collected After Cycles 8 & 11– Decision about eligibility for additional optional treatment

Approx. 2 wks later	Get routine blood tests, research tests, urinalysis and imaging tests; Serologic markers.
	Brief physical and update of medical history.
After every 3 Cycles	Fill out the "Quality of Life" questionnaire.

Optional Monthly Additional Phase - Cycles 9 through 14 (1 month apart)

Visit 1	Brief physical and update of medical history.
	Get routine blood tests.
	Fill out the "Quality of Life" questionnaire.
	Receive low-dose cyclophosphamide (Cytoxan).
Visit 2	Have DTH skin test injections in forearm.
	* Cycle # 9 and 12 only - Have Anergy test injections.
	Receive injections of SV-BR-1-GM into skin of right and left thighs and two places on the upper back.
Visit 3,4	Evaluation of SV-BR-1-GM injection sites.
	Receive Interferon-alpha-2b (Merck) injection into SV-BR-1-GM sites on 2 days (±1) and 4 days (±1) after SV-BR-1-GM.

Off-Treatment Evaluation Visit

About 6-12 months after 1st SV-BR-1-GM	Get routine blood tests, research tests, urinalysis and imaging tests; Serologic markers.
	Brief physical and update of medical history.
	Fill out the "Quality of Life" questionnaire.

9.1.2. HIPAA Authorization Form

RESEARCH CONSENT FORM ADDENDUM

DISCLOSURE OF YOUR PERSONAL HEALTH INFORMATION
You are being invited to be in a research study. As part of that study lots of data will be generated. Some of it will be your personal health information. If you don't authorize use or disclosure of your health information, you cannot participate in the study as it would not contribute to the outcome.

1. **WHO** can give out the information?

Principal Investigator or "Study Doctor"
[Investigators name]
Phone: (XXX) XXX-XXXX.

2. **WHAT** information may be disclosed?
   - Results of the experimental procedure
   - Laboratory results of tests done for the study
   - Study-related medical information

3. **TO WHOM and WHY** will the information above will be disclosed?
   - BriaCell Therapeutics Corp (Study Sponsor)
   - Cancer Insight (Clinical Research Organization running the trial)
   - The National Cancer Institute (NCI) and U.S. Food and Drug Administration (FDA), to audit.
   - The Institutional Review Board responsible for oversight of this research is entitled to inspect the above information.

Your personal health information may no longer be protected by the Privacy Rule if any of these groups re-disclose it to somebody else. (There could be other rules they must follow, however.)

4. **REVOCATION**: You may cancel this authorization at any time, by notifying the following person in writing to your study doctor

If you cancel this authorization, your health information collected during the study will only be used to make administrative or safety reports required by the study. You will also have to be withdrawn from the study.

5. **EXPIRATION:** This authorization will expire automatically at the end of the study.

6. **REFUSAL:** If you decline to sign this authorization, it will not affect regular, non-research treatment by your doctor, payment from your insurance, enrollment in any health plan, or eligibility for their benefits. However, you cannot participate in the study if you do not sign.

7. **ACCESS TO INFORMATION:** You may inspect and get a copy of the information disclosed under this Authorization.
8. **COMPENSATION:** There is no additional compensation provided to study doctor for the cost of obtaining this Authorization.

Participant's Signature and Investigator/Coordinator Signature:

	Participant: I am authorizing use of my health information in the way it is described above. After we sign this, I will get a copy.	**Person obtaining consent**: We will allow participant's information to be used only as described above. After we sign this, we will keep the original.
Printed Names		
Signatures		
Date / Time		

9.1.3. Consent for Use of Blood or Tissue for Research

CONSENT FOR THE USE OF BIOLOGICAL SPECIMENS FOR RESEARCH

Study Sponsor: BriaCell Therapeutics Corp.

PURPOSE	BriaCell would like your permission to use your tissue and/or other biological specimens for ongoing research in developing cancer treatments. The specimens will be collected from you by the study doctor or his/her staff, during your participation on this research study sponsored by BriaCell Therapeutics Corp.
PROCEDURES	The specimens will be collected during routine blood draws or urine collections. They will be stored in a deep freeze liquid nitrogen storage tank or freezer. The specimens will remain in the possession of BriaCell Therapeutics Corp and will not be transferred to any other researcher without your specific permission below.
CONFIDEN-TIALITY	The specimens will be stripped of all information that could identify you, and a code number assigned. The code number may link to certain clinical or other information about you that will be protected as best as possible by BriaCell Therapeutics Corp.
RISKS	There are no *physical* risks to you or anyone else. There is a remote possibility that information about you could be inadvertently disclosed in the process of conducting research. However, the risk is very small because your name and other identifying information will no longer be associated with the biological specimens.
BENEFITS	There will be no benefit to you. The knowledge gained by BriaCell could help cancer patients in the future. Your specimens and information will be combined with other specimens and used by scientists. You will not share in any profits that might result.
ALTERNATIVES	You can refuse to allow your specimens to be used by BriaCell for its own or outside research purposes. Please designate “yes” or “no” in the space provided below.
QUESTIONS	If you have any questions about the storage or use of your specimens, please contact your Study Site.
RIGHTS	You have the right to refuse to participate. If you agree, you have the right to withdraw your samples at any time. Simply contact your Study Site at the numbers above, and your samples will be re-identified and destroyed. If you refuse or withdraw there will be no penalty to you.

Participant's Signature - Please sign and date ONE section below:

YES - I agree to allow BriaCell Therapeutics Corp to conduct ongoing research on my biological specimens as explained on this form, including possible transfer to outside researchers.	**NO** - I do not want any more research done on my specimens than necessary for this study. Please destroy them after the tests are completed for the main study.
Your Signature:	**Your Signature:**
Your Printed Name:	**Your Printed Name:**
Today's Date:	**Today's Date:**

If you choose YES, to allow BriaCell Therapeutics Corp to conduct ongoing research on your biological specimens; please designate your decisions below, then sign and date.

Decisions for you to tell us about: (Check one answer per question)

1. □ Yes □ No Do you agree to donate specimens for this repository to be used for ongoing research by BriaCell Therapeutics Corp.?

2. □ Yes □ No Do you give permission for your biological specimens to be connected to your medical information by a code?

3. □ Yes □ No Is it OK for your biological specimens to be given by BriaCell Therapeutics Corp. to other researchers for further investigations?

4. □ Yes □ No Is it OK if the study site contacts you in the future about clinical information discovered as part of its ongoing research?

Your Signature:

Your Printed Name:

Today's Date:

9.1.4. Study Information Sheet

FREQUENTLY ASKED QUESTIONS ABOUT

SV-BR-1-GM

Principal Investigator (Study Doctor): As per the Study Site
Study Sponsor: BriaCell Therapeutics Corp

1. How is the SV-BR-1-GM made?
Tumor cells are collected from cancer patients. The cells are modified to produce GM-CSF, a biological medication widely used to stimulate the bone marrow production of white blood cells. The tumor cells are grown in special flasks and frozen. Just before use, the cells are thawed; the cell preparation is diluted, and then given a treatment with x-rays to nullify any further cell growth.

2. How is the SV-BR-1-GM given?
The SV-BR-1-GM is injected into the skin in four places, two places on the upper back and two places on the thighs (left and right).

3. How often is it given?
SV-BR-1-GM is given every 2 weeks for 3 times. Then the participant has repeat scans and/or x-rays to see any possible effect. Depending on the tumor response, the participant may then go onto a monthly booster schedule for more injections.

4. Do I have to be in the hospital?
No, the SV-BR-1-GM is designed to be given in a doctor's office.

5. What is GM-CSF and why is it needed?
GM-CSF is a biological medication widely used to stimulate the bone marrow production of white blood cells. There is, however, new data that this agent can also help generate a more effective immune response.

6. What are the side-effects of SV-BR-1-GM?
Side effects are uncommon. We have had no life-threatening events and have only rarely seen allergic reactions or incision infections. These have been mild and self-limited. You will not lose your hair or have vomiting from the SV-BR-1-GM. Nausea after the priming medicine, if it is occurs, is manageable with some of the newest anti-vomiting medicines. The SV-BR-1-GM is checked carefully for contamination, viruses, or infectious microbes. In theory, there is always a slight chance of some undiscovered or unpredicted side-effects.

7. Am I being experimented on?
Yes. As a research participant, you should know that this study was reviewed by a registered Institutional Review Board for compliance with medical ethics, safety, and scientific justification. The programs are then reviewed by the FDA and listed in the National Cancer Institute website. You should understand clearly that this program is a research investigation. We are trying to develop a new treatment, learn as much as possible, and hopefully help the patients who come to us. But this

is a research program, we cannot guarantee it will benefit you, and we must always be on the lookout for unpredicted or unexpected effects.

8. What is "informed consent?"

Before you decide to be in the study or begin any study procedures you will be given a document which explains in detail the program and any known or theoretical side effects as mentioned above. The document must be signed to indicate that you have been told the details of the program that you enter into it freely without pressure or deception, that you have been informed you can at any time ask further questions, and that you also have been informed about your rights and responsibilities as a research participant.

Signing the consent form does not take away any of your rights, including the right to change your mind. The consent process actually helps protect your rights and it also protects the ethical intent of our research.

9. How much does the SV-BR-1-GM cost?

We do not charge for the SV-BR-1-GM. You should be aware that there will be costs and charges, according to standard fees, for most study procedures including medical visits, for the doctor's visits where the SV-BR-1-GM and other study drugs are given, for laboratory and imaging tests, and for the supplies, needles and syringes, medications, etc. used in the study.

10. Will my insurance or Medicare cover these fees?

Generally, third-party payers routinely cover doctors' visits and routine charges. Depending on circumstances, some carriers will reimburse for expenses associated with the experimental treatment, but we cannot predict or guarantee you will be covered for all or part of the expenses. The sponsor and your doctors are committed to minimizing costs and to providing care and working with all eligible patients. The SV-BR-1-GM study is NOT subsidized by Federal funds. If you have special circumstances please be sure to discuss these with your doctors. Travel, lodging and other reasonable expenses may be reimbursed by the Sponsor when requested by the Investigator but must be pre-approved by the Sponsor.

11. I'd like to be part of this study. What do I do next?

Notify our office and information will be provided. We will need medical records, pathology reports, x-rays and scans, etc. We frequently like to discuss your medical situation with your personal physician. In evaluating your case we will try to make our recommendations as responsibly as possible.

USEFUL CONTACT INFORMATION:

Principal Investigator: [Investigator's name]
Phone: (XXX) XXX-XXXX.

You may also call the National Cancer Institute's Cancer Information Service at:

- 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

9.1.5. Screening Evaluation Form

SUGGESTED FORM TO DETERMINE FINAL ELIGIBILITY OF PARTICIPANT

Do not write participant's name or other identifying information on this form.

Step 1: Consent & Enrollment Procedure **Date:**

□ Consent form signed by subject and PI. □ All the subject's questions answered.

□ HIPAA form signed by subject and PI. □ CA Bill of Rights signed by subject and PI.

□ Proxy form signed by subject. □ Medical Release form signed by subject.

□ Supplement consent form regarding biological specimens signed by subject.

□ Privacy Notice provided to subject.

□ Copies of all signed forms provided to subject.

Step 2: Assign Study ID Number

Participant's Study ID Number: _____

Step 3: Inclusion /Exclusion Criteria **Date:**

□ Yes	□ No	Are all inclusion criteria met?
□ Yes	□ No	Does the participant meet any exclusion criteria?
□ Yes	□ No	In the investigator's determination, does this participant qualify to be in this study?

Explain any exceptions or deviations from protocol (notify the IRB):

Step 4: Screening Tests & Procedures

Is the subject eligible to be in this study, based on the results of:

Focused medical & social history

□ Yes □ No □ N/A

Date done:

Complete history physical exam & ECOG scale

□ Yes □ No □ N/A

Date done:

Blood tests

□ Yes □ No □ N/A

Date done:

Serum beta-HCG pregnancy test (within 7 days of SV-BR-1-GM start date)

□ Yes □ No □ N/A

Date done:

Immunohistological evaluation

□ Yes □ No □ N/A

Date done:

MRI or mammogram of the breast

□ Yes □ No □ N/A

Date done:

CT scan chest, abdomen and pelvis

□ Yes □ No □ N/A

Date done:

CA 125

□ Yes □ No □ N/A

Date done:

CEA, CA 27.29 (or CA 15-3)

□ Yes □ No □ N/A

Date done:

Urinalysis

□ Yes □ No □ N/A

Date done:

HL-A profile

□ Yes □ No □ N/A

Date done:

SF-36 Questionnaire

□ Yes □ No □ N/A

Date done:

Chest X-ray

□ Yes □ No □ N/A

Date done:

Isotope bone scan, and/or selected bone X-rays

□ Yes □ No □ N/A

Date done:

Brain scan MRI or CT technique

□ Yes □ No □ N/A

Date done:

Explain any non-eligibility factors, exceptions, or deviations from protocol (notify the IRB):

Step 5: Eligibility Status

□ Eligible Final eligibility status

□ Ineligible

If ineligible, what was the reason?

Step 6: Signatures

	Principal Investigator	**Person who collected information on this form**.
Printed Names		
Signatures		
Date / Time		

Step 7: FILE the original form in the study files for this participant.

9.1.6. Screening and Enrollment Log

This is a confidential form; to be used ONLY by the Principal Investigator, or his/her authorized designee. Keep this form in a locked filing cabinet when not in use. Enter information for all participants who are screened; whether or not they are eligible.

If Eligible: Write a sequential number, the Subject ID #, and status "Enrolled"

If Ineligible: Do NOT number. Provide the reason for ineligibility

Do not write participant's name or other identifying information on this form.

No.	Screening Date	Participant ID #	Status	Ineligible Reason	End Date Reason	Initial
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	
			□ Enrolled □ Ineligible □ Withdrawn		__________	

Principal Investigator: ___________________________________ Date: ___________

Checked by Monitor: ______________________________________ Date: ___________

9.2. SUBJECT MANAGEMENT FORMS

9.2.1. Subject Withdrawal Form

Participant's ID Number: _____ Withdrawal Date: _____

□ Participant's Decision Withdrawal reason(s):

□ Investigator's Decision
Other comments:

□ ***NOTE: Inform participant that this is the end of the study.***

	Principal Investigator	**Person who collected information on this form**.
Printed Names		
Signatures		
Date / Time		

9.2.2. Telephone Contact Log

All telephone calls to/from the Principal Investigator's office regarding this study, the date, time, and reason for the contact should be recorded, as well as who initiated the contact. Write a brief explanation of the resolution of the event, and follow the procedures for reporting any adverse events as needed.

Do not write participant's name or other identifying information on this form.

Date/ Time	Participant ID Number	Reason for Call / Resolution	Staff Initials

9.3. CLINICAL and DATA COLLECTION FORMS

Clinical and data collection forms record the protocol required information to be reported. The primary data collection instrument for the study is the eCRF. Essential eCRFs are listed:

- Medical and Surgical History CRF
- Physical Exam with Vitals and ECOG Performance Status CRF
- SF-36 QOL Questionnaire
- Demographics and Clinical Information CRF
- Concomitant Medications CRF
- Adverse Events CRF
- Full Labs CRF (includes CBC, CMP, Urinalysis, T&B subsets, Serological markers)
- CBS Lab CRF (CBC diff only)
- Baseline Tumor Assessment (RECIST and iRECIST criteria) CRF
- 3/6/9/12 Month Tumor Assessment (RECIST and iRECIST criteria) CRF
- Treatment Cycle Encounter CRF

9.4. REFERENCES

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9.4.2. Pharmaceutical Descriptions of Study Substances

Cyclophosphamide (Cytoxan®, CTX, CPM, Neosar®)

Classification: Alkylating agent

Mode of Action: Cyclophosphamide prevents cell division primarily by cross-linking DNA strands. The cell continues to synthesize other cell constituents (RNA and protein), an imbalance occurs and the cell dies. Cyclophosphamide is considered cell cycle, phase nonspecific.

Storage and Stability: Injectable forms are stable at room temperature for storage. It is recommended that temperature for storage not exceed 90ºF. Reconstituted solution is stable 24 hours at room temperature or 14 days if refrigerated when paraben-preserved diluent is used for reconstitution. Unused diluted drug should be discarded. Shake vials vigorously and warm slightly to facilitate dissolving of cyclophosphamide crystals. Vials may be immersed in lukewarm water to facilitate solution without risk of decomposition.

Dose and Administration: Cyclophosphamide 300 mg/m^2 (or a lower dose with the Sponsor's approval) given as a single dose over 1-2 hours by intravenous infusion. Premedication with antiemetics is permitted, provided no corticosteroids are included.

Interferon-alpha-2b (Merck)

Drug Information For: INTRON A 10 MIL IU SOLN SDV

Ingredient Name: INTERFERON (in-ter-FEER-on) ALFA-2b

Drug Manufacturer: MERCK

Common Uses: This medicine is an interferon used to treat certain types of leukemia, certain AIDS-related illnesses, and certain forms of hepatitis. It may also be used to treat other conditions as determined by your doctor.

Before Using This Medicine: WARNING: This medicine can cause or worsen some serious medical conditions including psychiatric conditions (e.g., depression), immune system problems (autoimmune conditions such as lupus or rheumatoid arthritis), and circulation problems (e.g., cardiovascular disease/blood clots), or infections (bone marrow suppression). If your medical history includes any of these conditions, inform your doctor promptly. Also, tell your doctor immediately if any serious symptoms or side effects occur (see Possible Side Effects section).

These conditions occur infrequently, but some can be fatal. Some medicines or medical conditions may interact with this medicine. INFORM YOUR DOCTOR OR PHARMACIST of all prescription and over-the-counter medicine that you are taking. ADDITIONAL MONITORING OF YOUR DOSE OR CONDITION may be needed if you are taking fluorouracil, zidovudine, barbiturates (e.g., phenobarbital), theophylline, vidarabine, other drugs that depress the immune system (e.g., anti-cancer type). Tell your doctor if you take any drugs that make you drowsy, such as: medicine for sleep (e.g., sedatives), tranquilizers, anti-anxiety drugs (e.g., diazepam), narcotic pain relievers (e.g., codeine), psychiatric medicines (e.g.,

phenothiazines such as chlorpromazine, or tricyclics such as amitriptyline), anti-seizure drugs (e.g., carbamazepine), muscle relaxants, and certain antihistamines (e.g., diphenhydramine). USE OF THIS MEDICINE IS NOT RECOMMENDED if you have a history of other severe liver conditions (e.g., autoimmune hepatitis, decompensated liver disease), or immune system suppression for organ transplants. Inform your doctor of any other medical conditions, including psychiatric conditions (e.g., depression), low blood cell counts (e.g., red cells, white cells, or platelets), heart problems, thyroid problems, lung diseases (e.g., COPD, asthma, pneumonia), intestinal disease (e.g., colitis), pancreatitis, immune system diseases (e.g.,

lupus, rheumatoid arthritis), eye problems, diabetes, kidney disease, high blood pressure, brain tumors, seizures, allergies, pregnancy, or breast-feeding. Contact your doctor or pharmacist if you have any questions or concerns about taking this medicine.

How to Use This Medicine: Follow the directions for using this medicine provided by your doctor. This medicine comes with a medication guide. Read it carefully. Ask your doctor, nurse, or pharmacist any questions that you may have about this medicine. This medicine is sometimes used at home as an injection. Before using this medicine, a healthcare professional will provide detailed instructions for its appropriate use. This medicine comes with a patient information leaflet. Read it carefully. Ask your doctor, nurse, or pharmacist any questions that you may have about this medicine or giving injections. USE THIS MEDICINE AT BEDTIME unless directed otherwise. DRINKING EXTRA FLUIDS while you are taking this medicine is recommended. Check with your doctor or nurse for instructions. STORE THIS MEDICINE as directed on the prescription label. Do not use this medicine if it is cloudy or discolored. ANY LEFTOVER MEDICINE or supplies used with this medicine should be placed in a plastic bag and disposed of as instructed by your doctor, nurse, or pharmacist. IF YOU MISS A DOSE OF THIS MEDICINE, check with your doctor for further instructions. Do not use 2 doses at once.

Cautions: KEEP ALL DOCTOR AND LABORATORY APPOINTMENTS while you are taking this medicine. DO NOT CHANGE BRANDS OF THIS MEDICINE without discussing it with your doctor. THIS MEDICINE MAY CAUSE dizziness. Do not drive, operate machinery, or do anything else that could be dangerous until you know how you react to this medicine. THIS MEDICINE WILL ADD TO THE EFFECTS of alcohol and other depressants. Ask your pharmacist if you have questions about which medicines are depressants. BEFORE YOU HAVE DENTAL WORK, check with your doctor. IF YOU EXPERIENCE difficulty breathing; tightness of chest; swelling of eyelids, face, or lips; or if you develop a rash or hives, tell your doctor immediately. Do not take any more doses of this medicine unless your doctor tells you to do so. FOR WOMEN: IF YOU PLAN ON BECOMING PREGNANT, discuss with your doctor the benefits and risks of using this medicine during pregnancy. IT IS UNKNOWN IF THIS MEDICINE IS EXCRETED in breast milk. DO NOT BREAST-FEED while taking this medicine.

Possible Side Effects: SIDE EFFECTS, that may go away during treatment, include flu-like symptoms of fever, chills, headache, fatigue, muscle/joint aches, loss of appetite, nausea or vomiting, diarrhea, or stomach pain; temporary hair loss; or change in taste. If they continue or are bothersome, check with your doctor. CONTACT YOUR DOCTOR IMMEDIATELY if you experience drowsiness, dizziness, difficulty sleeping, one-sided weakness (arm/leg), vision changes, poor coordination, irregular heartbeat, intolerance to heat or cold, black stools,

persistent sore throat, chest tightness, unusual bleeding/bruising, tingling hands or feet, yellowing of the eyes or skin, dark urine, seizures, change in amount of urine, unusual increase in thirst, or severe stomach/abdominal pain. CONTACT YOUR DOCTOR IMMEDIATELY AND STOP YOUR TREATMENT with interferon if you experience any of the following: unusual or severe mental/mood changes (e.g., suicidal thoughts or severe depression), or bloody diarrhea. IF YOU EXPERIENCE difficulty breathing; tightness of chest; swelling of eyelids, face, or lips; or if you develop a rash or hives, tell your doctor immediately. Do not use any more doses of this medicine unless your doctor tells you to do so. If you notice other effects not listed above, contact your doctor, nurse, or pharmacist.

9.4.3. SV-BR-1-GM Preparation

1. Establishment and characteristics of parental breast carcinoma cell line (SV-BR-1):

The parental cell line was established in 1999 from a chest wall mass occurring in a 36-year old woman, married, a mother of 2 children, with no known history of or risk factors for sexually transmitted disease. The patient had previously-diagnosed breast cancer metastatic to brain, bone, lung, and skin. A single-cell suspension was created by collagenase digestion and the cells grown in tissue culture according to standard techniques. Both the cell line and the biopsy from which the cell line was derived were consistent with metastatic breast cancer by pathology and grew in soft agar. The cells grew as an epithelial, adherent monolayer culture, were passaged over 50 times with doubling time of 48 hours. The cell line is negative for estrogen receptors as was the original metastatic tumor specimen, and has a human female karyotype. Histochemical stains show reactivity with anti-keratin antibodies and strong expression of the HER-2/neu antigen. The cell line grew readily in the nude mouse and the resultant tumors had the histological appearance of human breast cancer and showed positivity for human beta-actin by PCR[1]. The original Master Cell Bank (MCB) for the SV-BR-1 cell line has been established and tested for sterility, mycoplasma, T. pallidum, and human pathogens. Source documents for all the above have previously been submitted for the approved clinical trial, BB-IND 10312, and may be provided upon request.

2. Transformation of *E. coli* with GM-CSF Plasmid:

Transformation of Ready Made Competent Top 10 E.coli bacteria with pcDNA 3.1 /GS/GM-CSF Plasmid. The Genestorm hORF (human open reading frame) Expression Vector pcDNA 3.1/GS kit that includes competent Top 10 E.coli bacteria was purchased from Invitrogen (Catalog #H-M13207M). The bacteria were transformed with supplied pcDNA 3.1/GS plasmid containing a human GM-CSF ORF (open reading frame) and a zeocin-resistance gene. The GM-CSF ORF was sequenced and insertion of the GM-CSF ORF was confirmed. However, also 2 variations from the NCBI Reference Sequence of GM-CSF (NP_000749.2) were detected, one at position 53 (Thr instead of Met) and the other at position 117 (Thr instead of Ile). Whereas position 53 mapped between the first beta-pleated sheet (amino acids 39-43) and the second alpha helix (amino acids 55-64), and was not implicated in binding of GM-CSF to the receptor alpha subunit, position 117 mapped to a region associated with receptor binding (Eur J Biochem. 1994;225(3):873-80), thus raising the question of whether receptor binding and thereby signaling can still occur with the threonine at position 117. In agreement with signaling activity and thus

[1] Medical Diagnostic Laboratories LLC, Mt. Laurel, NJ

GM-CSF bioactivity, cell culture supernatant from irradiated SV-BR-1-GM cells supported the proliferation of MUTZ-3 cells, a cell line reported to depend on cytokines such as GM-CSF (Leukemia. 1996;10(6):1025-40), whereas supernatant from parental SV-BR-1 cells (not engineered to express GM-CSF) had at most a minimal effect (data not shown).

The map of the pcDNA3.1/GS plasmid indicates that the GM-CSF ORF in mammalian cells is driven by a CMV promoter. The bacteriophage T7 promoter upstream of the GM-CSF ORF is not expected to be functional in mammalian cells. In addition to the GM-CSF coding sequence (CSF2 gene), the GM-CSF ORF also contains, at the 3' end, a sequence encoding a V5 epitope tag and a polyhistidine (6xHis) tag. The entire GM-CSF ORF is thus expressed as a fusion protein in mammalian cells. The map also shows that the plasmid is expected to be safe as it does not have a replication origin or coding sequences for nuclear antigen to permit extrachromosomal replication in human.

3. Selection of transformed *E. coli*:

The transformed bacteria were selected on Zeocin agar plates (Invitrogen; Q621-20), expanded in liquid Zeocin media (Invitrogen; Q620-20), mixed with equal amount of glycerol (Gibco, 15514-011)-SOB Media (Sigma H8032), aliquoted and stored in the -70°C freezer.

4. Extraction of pcDNA 3.1 /GS/GM-CSF from transformed *E. coli*:

The frozen transformed E. coli was expanded in Zeocin Liquid media. The extraction of the pcDNA3.1/GS plasmid was carried out using Invitrogen's S.N.A.P. Miniprep Kit (Cat #K1900-25) following the manufactures instructions. The extracted plasmid was aliquoted and stored in the -70°C freezer.

5. Evaluation of quantity and purity of the extracted plasmid:

The quantity and purity of the extracted plasmid was determined by spectrophotometer. The plasmid sample was analyzed at 260 nm to determine the total yield of plasmid DNA and at 280 nm to assess the amount of contaminating proteins. The 260/280 ratio for the plasmid lot used for transfection was 1.7 (1.5 ratio is commonly accepted as a "cut-off" level of DNA purity).

6. Evaluation of integrity of the extracted plasmid:

The integrity of the extracted plasmid DNA was analyzed by gel electrophoresis. The samples were serially diluted 1:2 with sterile distilled water. For each lot of plasmid seven serial dilutions were prepared and ran along with 1 kb DNA ladder (Promega, Cat # G5711). The gel was stained with SYBR Gold Nuclei Acid Gel Stain and viewed using VisiBlue Transilluminator. The plasmid lot used for transfection of SV-BR-1 cells appeared as a single band of approximately 3,000 bp and no lighter bands have been detected suggesting integrity of a tested plasmid. The anticipated size of the plasmid according to manufacture (Invitrogen) is 4,000 bp. The difference can be explained by the circular shape of the plasmid compared to the linear DNA present in the ladder that may result in changed gel motility. The additional heavy bands can be explained by multiple plasmid DNA particles present in the sample.

7. Assessment of parental SV-BR-1 cell line sensitivity to Zeocin:

For selection of successfully transfected tumor cells the parental breast carcinoma (SV-BR-1) cells were cultured in the presence of various concentrations of Zeocin to determine the minimal concentration that kills most of the nontransfected cells.

8. Transfection of SV-BR-1 with pcDNA 3.1/GS/GM-CSF plasmid:

SV-BR-1 (passage 27) cells were harvested using 0.25% Trypsin – 0.53 mM EDTA (Gibco, Cat # 25200, lot 1059547). The cells were seeded in a 12-well plate and incubated for forty-eight hours. Following incubation the cells were transfected with the pcDNA 3.1/GS/GM-CSF plasmid using LipofectAMINE 2000 reagent (Gibco, Cat #18292-011) according to the manufacturer's directions. The cells were incubated with the transfection solution in the antibiotic free RPMI-10% FBS (Fetal Bovine Serum) (FBS, Irvine Scientific #3003, lot 300390135; RPMI, Irvine Scientific #9160, lot 916081255) for 24 hours

9. Selection of permanently transfected SV-BR-1-GM clones and establishment of the SV-BR-1-GM cell line:

The permanently transfected tumor cells were selected by culturing in the RPMI-10% FCS containing 10 ⌈g/ml Zeocin (selective media) for approximately one month. The surviving colonies were propagated in T-12, T-25, and T-75 flasks using selective mediator to establish a permanently transfected cell line (SV-BR-1-GM). After a few successful passages, the concentration of Zeocin in the media was decreased by roughly 50% to 4 ⌈g/ml (maintenance media). The supernatant of cultured transfected tumor cells was tested for GM-CSF production by ELISA assay and found positive. The early passages of the SV-BR-1-GM cell line were frozen by staged freezing in a controlled rate device via –70º C freezer for 24h prior to final storage in a liquid nitrogen freezer.

10. Preparation and validation of the original SV-BR-1-GM Master Cell Bank (MCB):

SV-BR-1-GM cells (passage 4) was propagated in T-25, T-75, and T150 flasks using maintenance media (FBS, Irvine Scientific #3003, lot 300390135A; RPMI, Irvine Scientific #9160, lot 916010673). To confirm the production of GM-CSF, randomly selected flasks were incubated with the antibiotic-free RPMI-10% FBS for 72 hours. The supernatant was collected and the concentration of GM-CSF was determined by ELISA. The results showed that the GM-CSF is produced by cultured SV-BR-GM cells at the average concentration of 305.57 ng/ml.

Biological activity of the released GM-CSF was established by evaluating proliferation of MUTZ-2 cells as assessed by 5-bromo-deoxyuridine incorporation, using flow cytometry. This leukemic line has sensitive growth-dependence on GM-CSF or other factors. Serial dilutions of supernatant of SV-BR-1-GM cells, with appropriate positive and negative controls, demonstrated mitotic activity comparable to positive controls.

The propagated cells were harvested using 0.25% porcine Trypsin – 1 mM EDTA (Gibco #25200, lot 1128850). The total yield was $115x10^6$ cells at a viability of 97%. The cells were resuspended in the freezing medium (10% Dimethyl Sulfoxide, Sigma, #D2650, lot 111K2340 in the antibiotic-free RPMI-5% Human Albumin) aliquoted into 77 cryovials at the concentration of $1.5x10^6$ viable cells/vial. The aliquots of a final product (before the freezing) were submitted for safety testing described next.

11. Safety and Sterility:

General sterility testing of the original SV-BR-1-GM master cell bank did not show evidence of contamination (testing according to 21CFR 610.12 performed by the Pathology Department of

St. Vincent Medical Center). Endotoxin testing performed in our laboratory was within acceptable limits.

Mycoplasma testing performed by culture at Specialty Laboratories, Santa Monica, CA did not show evidence of contamination, nor did parallel immunofluorescence testing done in our laboratory.

No mycoplasma, trypanosomes, or other pathogens were identified by electron microscopy performed by Dr. Linda Kelly, Diagnostic Laboratory, USC.

Treponema pallidum testing, performed on the cell line by qualitative PCR by Medical Diagnostic Laboratories LLC, Mt. Laurel, NJ, did not show evidence of contamination.

Also, one vial of MCB was taken for expansion in the antibiotic-free RPMI-10% FCS media for testing of HIV, HBV, HCV, and Human Parvo-virus performed by National Genetics Institute (Los Angeles, CA), HTLV, EBV, CMV, *in vitro* and *in vivo* adventitious agents performed by Apptec Laboratory Services (Camden, NJ). The results of all tests were negative and the level of endotoxin in the MCB sample was 0.0176 ng/ml, which is much less than the commonly accepted "cut-off" level of 1 ng/ml.

12. SV-BR-1-GM lot release preparation and validation:

Each lot of SV-BR-1-GM will be prepared by expansion of cells from one or several vials of a frozen SV-BR-1-GM Master Cell Bank (MCB). Expansion and other cell processing steps will be conducted under GMP conditions at the University of California, Davis (UC Davis) GMP facility at the Institute for Regenerative Cures (Sacramento, CA).

13. Product Shipping Conditions:

Tested and released lots of SV-BR-1-GM will be adequately packed with proper temperature controls and shipped via courier from the UC Davis GMP facility (Sacramento, CA) to the clinical sites. A data logger recording the temperature during transport will accompany each shipment. SV-BR-1-GM formulations will either be transported to the clinical sites as "liquid" product or as cryopreserved product in dry ice. For the former product, SV-BR-1-GM cells will be irradiated and resuspended in lactated Ringer's solution (LRS) and shipped on wet ice or other established temperature condition(s). For the latter product, SV-BR-1-GM cells will be irradiated and resuspended in biocompatible freeze medium then cryopreserved. Whereas SV-BR-1-GM transported as liquid product will need to be formulated hours before the inoculation, SV-BR-1-GM transported as frozen product will be provided to the investigator sites (clinical sites) at least 2-3 days in advance of the inoculation. For such frozen product, upon delivery via courier to the clinical site, the vials of SV-BR-1-GM will be inspected and transferred to an appropriate LN2 storage dewar at the site. For shipments of liquid or frozen product, minimum and maximum transport temperatures will be retrieved from the data logger. Thereafter, the data logger will be returned to the UC Davis GMP facility and additional temperature data will be reviewed. In the event that the minimum and/or maximum temperature(s) deviate(s) from the specified range, the SV-BR-1-GM formulation will not be used and will be returned to the UC Davis GMP facility or destroyed at the clinical site. SV-BR-1-GM transported as liquid product will be shipped via same-day courier to the clinical sites on wet ice or under other established temperature condition(s). All steps will be performed in accordance with approved UC Davis and BriaCell Therapeutics SOPs.

14. Product Tracking:

SV-BR-1-GM is tracked during the manufacturing process according to approved procedures and maintained in dedicated liquid nitrogen storage tank(s) during quarantine. Upon receipt of acceptable test results consistent with product release, SV-BR-1-GM is maintained at locations in the vapor phase of liquid nitrogen storage tank(s) dedicated to approved and released SV-BR-1-GM. The required number of vials will be removed upon request and prepared at UC Davis for in-house formulation or shipment to the clinical site as already formulated product, and verified by both qualified manufacturing and quality assurance personnel. Shipping and Quality Assurance documentation will be completed and forwarded to the site together with the vials of SV-BR-1-GM. Upon receipt and inspection of the SV-BR-1-GM vials, the number of vials and corresponding identification numbers will be verified prior to storage or immediate use. The recipient will complete the UC Davis chain of custody form as verification of receipt. At the completion of enrollment, unopened vials of SV-BR-1-GM will be returned to BriaCell or UC Davis for reconciliation, use for research projects, and/or destruction according to approved procedures. BriaCell and/or UC Davis will track vials of SV-BR-1-GM, according to lot number and other identifiers, from the initiation of manufacture through return to the GMP facility or to BriaCell, and to release for research projects or destruction.

15. SV-BR-1-GM formulation:

15.1 SV-BR-1-GM cryopreserved before irradiation

Process 1 (for SV-BR-1-GM not serum-starved prior to cryopreservation)
In summary, a suitable number of validated SV-BR-1-GM cells (at least approx. 30 million cells) vials will be removed from liquid nitrogen storage, thawed, cultured for 2-4 days in full medium (RPMI-1640, 10% FBS, GlutaMAX™), serum-starved for 24 hours, enzymatically detached using trypsin, and resuspended in phosphate-buffered saline (PBS).

Process 2 (for SV-BR-1-GM serum-starved prior to cryopreservation)
In summary, a suitable number of validated SV-BR-1-GM cells (at least approx. 30 million cells) vials will be removed from liquid nitrogen storage, thawed, and washed/resuspended in PBS.

For both Process 1 and 2, total cell counts and viability will be determined. For preparations with a viability of >70%, cells, in PBS, will be irradiated to 20,000 cGy (200 Gy) (dose applied previously), or to an alternative dose ensuring cell replication-incompetency, with an approved Cesium-source or alternatively in Varian Linac IX, medically approved for radiation therapy. Processing will be performed at UC Davis using aseptic GLP and GMP practice.

Irradiated SV-BR-1-GM cells will be resuspended to a concentration of ~10 x 10^6/mL in Lactated Ringer's Solution (LRS) solution and aliquoted into 2 mL cryovials (between ~0.5 and ~1.5 mLs per cryovial) which will be placed in a plastic specimen bag. The remaining cell suspensions will be retained at the manufacturing facility and used for Gram staining, endotoxin, and 14-day sterility testing. The Gram staining and endotoxin assessments will be performed prior to SV-BR-1-GM administration. Only lots that pass both the Gram stain and endotoxin tests will be injected. "14-day" sterility cultures will be observed on several days after SV-BR-1-GM injection and will be continued until about 14 days after SV-BR-1-GM injection to confirm sterility. Each case of SV-BR-1-GM contamination will be reported to the investigator and the

IRB/FDA. A positive culture action plan has been established to mitigate the risk to patients injected with SV-BR-1-GM that failed the sterility test.
For the transport to the clinical site, the vials will be labeled with information to include the nature of the contents [(SV-BR-1-GM or the parental cell line, BriaTest™ (SV-BR-1)] as well as the patient identification number, date of birth, the name of the investigator and that this is for investigational use only. In addition, the specimen bag will be labeled with information to include the nature of the contents (SV-BR-1-GM or the parental cell line, BriaTest™), the study identification number (ID), subject ID, the subject's date of birth, Lot Number, Date of Manufacture, Expiration date, the investigator's name and a statement, "Caution: New Drug Limited by Federal Law to Investigational Use". This will then be transported to the investigational treatment site in a Styrofoam box with cold packs to obtain a temperature of 2-8° C or under other established temperature condition(s) and utilized within 24 hours. At the investigative site, the SV-BR-1-GM will be distributed into syringes for injection as per Section 3.3 of this protocol.

15.2 Off-the-shelf product (SV-BR-1-GM cryopreserved following irradiation)

Cells from one or several vials of a Master Cell Bank (MCB) or a Working Cell Bank (WCB) of SV-BR-1-GM will be expanded to a lot of Clinical Product (CP), serum-starved for 24 hours, irradiated with 20,000 cGy (200 Gy) (dose applied previously), or to alternative dose ensuring cell replication-incompetency, and cryopreserved in a biocompatible freeze medium. Vials of this CP will be shipped from the UC Davis GMP facility to the clinical site(s) as described above. After thawing and prior to inoculation, the content of the CP vials will either be diluted with LRS or another suitable medium to reduce the concentration of the cryopreservative (e.g., DMSO) or injected undiluted. CP will be handled aseptically, including mixing to dissolve potential loosely adherent cells ("clumps"). The final concentration of cells will be adjusted so that no more than 2 mLs (4 x 0.5 mL) are inoculated.

15.3 Parental Cells (SV-BR-1)

"Parental Cells" (SV-BR-1), i.e., cells not stably transfected with *CSF2*, the gene encoding GM-CSF, needed for hypersensitivity testing, will be formulated following, in essence, the same procedure as for SV-BR-1-GM described above.

16. Formulation Laboratory SV-BR-1-GM Accountability:

Each SV-BR-1-GM preparation will be documented on the SV-BR-1-GM preparation form. The record will include the date, the number of vials thawed, SV-BR-1-GM lot number, and the number of cells per vial. All SV-BR-1-GM vials will be kept in a secure cryopreservation tank in a locked room with access limited to only authorized personnel. Each SV-BR-1-GM vial used will be documented in the liquid nitrogen tank log. The record will include the date, purpose of using, and the initials of the person removing the vial. In addition, the used SV-BR-1-GM description and location in the tank will be documented on the SV-BR-1-GM formulation form. A copy of this form will be filed in the sponsor's research files. The discarded SV-BR-1-GM lots will be documented on the discard form.

SV-BR-1-GM preparation (formulation) is initiated only after receipt of a written request by the sponsor, their designate, or the investigator for SV-BR-1-GM administration for one or several specific, qualifying, consented patient(s).

17. Clinical Site SV-BR-1-GM Accountability:

With the submission of the vials containing cryopreserved or liquid SV-BR-1-GM or Parental Cells (for hypersensitivity testing) to the investigator for injection, the person transferring the vials will sign a SV-BR-1-GM Accountability form indicating time, place, and date of the transfer. The receiving person will counter-sign this transfer procedure.

No SV-BR-1-GM will be provided to any clinician or scientist not involved with the study, and no patients except those formally enrolled in this protocol will receive SV-BR-1-GM. All personnel involved in the study will receive in-service training regarding these and other aspects of Good Clinical Practice. Only trained clinical personnel (MD, PA, RN, or others trained by them) will perform the injections.

9.4.4. CTCAE v4.03 Toxicity Criteria

(Standard reference – not provided)

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

9.4.5. Positive Culture Action Plan

In the case of a positive culture on drug product, the following steps will be taken:

1. The testing laboratory will notify the medical monitor or, if unavailable, their designate.
2. The medical monitor or their designate will contact the investigator and notify them of the positive culture result. The investigator will be requested to contact the patient immediately and ask whether there have been any signs of infection (local or systemic).
3. If the patient is not reporting any signs or symptoms of infection, an unscheduled visit to the clinical site will be performed as rapidly as feasible and the patient will be evaluated by the investigator. This evaluation will include, at the minimum, vital signs, physical examination (with close attention to the inoculation sites), Heme profile and differential, metabolic panel, blood and urine cultures.
4. If the patient is reporting any signs or symptoms of infection, appropriate treatment will be instituted immediately under the supervision of the investigator. The event will be written up as a Serious Adverse Event for reporting to regulatory agencies.
5. In parallel, the testing laboratory or another CLIA-certified laboratory will perform identification of the organism and antibiotic sensitivity analyses. These results will be communicated back to the medical monitor, or their designate, and to the investigator.