Initial safety and efficacy of a phase I/IIa trial of a modified whole tumor cell targeted immunotherapy in patients with advanced breast cancer

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ABSTRACT

Background: SV-BR-1-GM is a GM-CSF transfected breast cancer cell line which expresses HLA class I & II antigens. In a previous clinical trial, a partial response of widely metastatic breast cancer was seen in a patient who matched SV-BR-1-GM at HLA-DRB3*02:02. Here we report the safety and efficacy analysis with immunologic correlates of response in the initial patients in a phase I/IIa trial of SV-BR-1-GM in patients with advanced breast cancer

Methods: This phase I/IIa trial enrolled patients with recurrent and/or metastatic breast cancer refractory to standard chemotherapy/targeted-therapy. Patients received low-dose cyclophosphamide 2-3d prior to intradermal injection of SV-BR-1-GM (20x106 cells divided into 4 sites) and interferon-α into the inoculation sites (10,000 IU/site) ~2 & 4 days subsequently. Cycles were 2 weeks x3 then q mo x 3. Adverse events (AE) was evaluated after each inoculation and graded via CTCAE v4.03. Immunologic response was measured by delayed type hypersensitivity (DTH) after each inoculation. Disease response was evaluated radiographically q3 mo and as clinically indicated. (clinical trial NCT03066947).

Results: To date, twenty-two patients have been enrolled and 17 have been inoculated for a total of 39 SV-BR-1-GM inoculations given. Per inoculations, the maximum related AE was grade 1 in 64%, grade 2, in 7.7%, and grade 3 in 7.7%. There were no related grade >3 or unexpected AE. Efficacy data is available on the first six (Table). Tumor regression was seen in 2 patients. 01-002 presented with liver, bone and 20 classic miliary lung metastases (up to 9mm). This subject previously received 7 chemotherapy regimens. She matched SV-BR-1-GM at Class I & II HLA loci. Imaging at 3 mo showed virtually complete regression of all 20 identifiable lesions in the lungs. This response was maintained at 6 mo but the subject was taken off protocol because of disease progression (liver and bone). 01-005, matching HLA-A*24:02, had notable regression of cutaneous lesions, but progressed in pleural and pericardial effusions, had irreversible cardiac arrest (unlikely related). DTH increased in 01-002 from 4mm (first dose) to 47mm (8th dose). Three of 3 patients evaluated developed antibodies responses (as measured by flow cytometry with SV-BR-1) including 01-002. Interleukin 8 also increased in 01-002.

Conclusions: SV-BR-1-GM in this regimen appears to be safe and well-tolerated. In this initial exploratory analysis, SV-BR-1-GM can produce regression of pre-treated metastatic breast cancer correlating with an immunologic response. HLA matching is being evaluated as a predictor of response.

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

BACKGROUND AND OBJECTIVES

- SV-BR-1-GM is a breast cancer cell line with features of an antigen presenting cell including expression of Class II HLA molecules.
- Prior investigation indicates that patients who match SV-BR-1-GM at 1 or more HLA alleles may be more likely to respond to treatment
- Study 1: The SV-BR-1-GM regimen includes: low dose cyclophosphamide to reduce immune suppression (300 mg/m^2 2-3 days prior to inoculation); 20-40 million irradiated SV-BR-1-GM cells intradermally; and interferon-α2b (10,000 IU x 4) into the inoculation sites 2&4 days later with cycles are every 2 weeks x3 then monthly.
- Study 2: pembrolizumab (200 mg IV) in combination with the regimen from Study 1 with cycles every 3 weeks
- The objective is to evaluate the safety, preliminary efficacy and pharmacodynamic activity of the SV-BR-1-GM regimen alone or in combination with pembrolizumab

RESULTS – Study 1 "Monotherapy"

Study 1 Patient Population

Characteristic	No HLA Allele Matches (n=10)	1+ HLA Allele Matches (n=13)	2+ HLA Allele Matches (n=3)
Age (n=23)	58 ± 12	59 ± 9	71 ± 5
Median Prior Systemic Regimens (n=16: 9/10/3)	4 (range 1-13)	4 (range 3-7)	4 (range 3-7)
% ER/PR + (n=16: 5/11/3)	56%	50%	67%
% Her2/neu + (n=16: 5/11/3)	56%	30%	33%
% Triple Negative (n=16: 5/11/3)	22%	30%	0%

Conclusion: The patients are heavily pre-treated and generally similar regardless of HLA matching

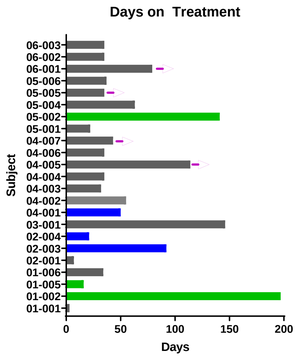
Adverse Events seen in 2 or More Patients

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Erythema	34				
Fatigue	4	1			
Flu Like Symptoms	2	1			
Injection Site Reaction	3				
Constipation	3				
Diarrhea	3	1			
Increased Peritoneal Fluid		2			
Nausea	3				
Sensory Neuropathy	2				
Induration	23				
Pruritus	10	2			
Rash	2				
Urticaria	3				

Serious Adverse Events

Body System	AE Term	Severity	Related to SV-BR-1-GM?
Respiratory	Respiratory Failure	Grade 4	No
Cardiac	Restrictive Cardiomyopathy	Grade 5	No
Nervous System	Dizziness	Grade 2	No
Respiratory	Pleural Effusion	Grade 4	No
Metabolism and nutrition disorders	Dehydration	Grade 3	No

Conclusion: The SV-BR-1-GM Regimen generally appears Safe and Well-Tolerated

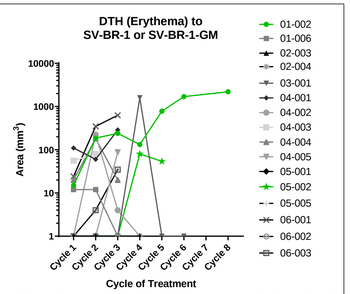


Green bars indicate patients with objective evidence of tumor regression
Blue bars indicate patients with decreased circulating Cancer-Associated Macrophage-like Cells (CAMLs) compared to baseline
Arrows → indicate the patients rolled over to combination therapy

HLA Matching and Biological Activity

Number of HLA Matches	0	1+	2+
Allele Match Between Patient and SV-BR-1-GM			
Number of Patients	10	13	3
Number with Tumor Regression	0	3	1
Number with Decreased CAMLs	1	3	2
Group or Allele Match Between Patient and SV-BR-1-GM			
Number of Patients	8	15	6
Number with Tumor Regression	0	3	2
Number with Decreased CAMLs	1	3	2

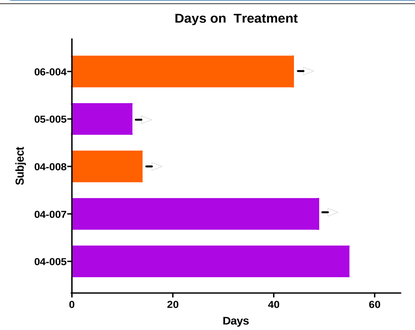
Conclusion: Patients who match SV-BR-1-GM at one or more HLA allele are more likely to show objective evidence of tumor regression and/or decreases in circulating cancer-associated macrophage-like cells (CAMLs), which have been shown to correlate with tumor stage.



DTH (length x width of erythema or induration) to 1x10^6 SV-BR-1 or SV-BR-1-GM cells was measured. Patients with tumor regression are shown in green. 60% of patients were anergic (Candida) at baseline but 59% developed DTH during the study to SV-BR-1/SV-BR-1-GM.

Conclusion: Most patients developed DTH to SV-BR-1/SV-BR-1-GM in spite of a high frequency of anergy. Those with tumor regression had robust DTH responses.

RESULTS – Study 2 Pembrolizumab Combination



Purple bars indicate roll-over subjects from Study 1
Orange bars indicate new patients
Arrows → indicate ongoing subjects in the study

To date treatment has been generally safe and well tolerated with no serious adverse events (AEs) or withdrawals from AEs.

Conclusion: The combination of the SV-BR-1-GM regimen with pembrolizumab has been safe. The study is ongoing.

CONCLUSIONS

- All patients with evidence of tumor regression and 3 of 4 with decreases in CAMLs match with SV-BR-1-GM at 1 or more HLA loci
- Delayed Type Hypersensitivity to SV-BR-1 is present in most patients after several cycles of treatment and the most robust response was seen in a patient with regression of multiple pulmonary metastases
- Initial data on the combination of the SV-BR-1-GM regimen with pembrolizumab suggests the combination is safe and well tolerated

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