Efficacy and safety of a modified whole tumor cell targeted immunotherapy in patients with advanced breast cancer alone and in combination with immune checkpoint inhibitors

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ABSTRACT

Background: SV-BR-1-GM is a GM-CSF transfected breast cancer cell line, exceptional for having antigen-presenting capability expressing both HLA I and II. We report clinical efficacy, safety, and immunologic correlates of response from our initial Phase I/II trial and initial data from our trial of SV-BR1-GM in combination with immune checkpoint inhibitors.

Methods: We enrolled patients with recurrent and/or metastatic breast cancer refractory to standard therapy. Patients received cyclophosphamide 300 mg/m^2 2-3d prior to intradermal injection of SV-BR-1-GM (20-40x10^6 cells divided into 4 sites) and IFNα into the inoculation sites (10,000 IU/site) ~2 & 4 days subsequently. Cycles were q2 weeks x3 then qmo x 3. Adverse events (AE) were evaluated after each inoculation. Immunologic responses were measured by delayed type hypersensitivity (DTH) after each inoculation with humoral and cellular responses evaluated ~q3 mo. Disease response was evaluated radiographically q3 mo and as clinically indicated (clinical trial NCT03066947). A similar regimen was used with SV-BR-1-GM in combination with pembrolizumab (200 mg IV) with cycles every 3 weeks (Phase I/II study NCT03328026).

Results: In Phase I/IIa (NCT03066947), 23 patients underwent 1-8 cycles of treatment. Tumor regression was seen in 3 patients, all of whom matched SV-BR-1-GM at least at one HLA allele. There were no related serious adverse events. The most common adverse event was minor local irritation at the inoculation site. Clinical data are shown in the table. A measurable DTH response was present in 21 patients. Of patients who developed a DTH response and had at least one HLA match, the tumor regression rate was 33% and for those with 2 HLA matches 67%. We saw evidence of antibody responses in 3 of 5 patients evaluated to date. Especially in responders after treatment, blood lymphocytes showed increased cytokine secretion (including ITAC, IFNγ, IL-6 & IL-8) following stimulation with antigens expressed in SV-BR-1-GM. 21/23 patients had expression of PD-L1 in identified circulating cancer-associated cells, and expression levels increased with treatment. Therefore, a combination study with pembrolizumab was initiated. Data on the first 6 patients shows that the regimen is clinically active and safe. One patient with a robust DTH response had evidence of tumor regression in liver metastases. This study is ongoing and is being modified to evaluate combination therapy with the PD-1 inhibitor INCMGA00012 and the IDO inhibitor epacadostat.

Conclusions: SV-BR-1-GM appears to be safe and well-tolerated. Contrary to conventional wisdom, SV-BR-1-GM can produce regression of metastatic breast cancer correlating with an immunologic response and HLA matching. Combination therapy with checkpoint inhibitors is ongoing.

	Patient Characteristics - Monotherapy		
HLA matches	None (n=6)	1+ (n=17)	2+ (n=5)
Age	55 ± 14	60 ± 8	66 ± 7
Median Prior Systemic Regimens	6 (range 2-13)	4 (range 1-7)	4 (range 3-7)
% ER/PR +	67%	46%	75%
% Her2/neu +	33%	46%	50%
% Triple Negative	33%	23%	0%
% Grade I or II	2/6 (33%)	4/16 (25%)	2/5 (40%)
Tumor Regression	0	3 (18%)	2 (40%)
DTH Response	2/6 (33%)	9/15 (60%)	3/4 (75%)
Tumor Regression in DTH Responders	0/2 (0%)	3/9 (33%)	2/3 (67%)
Tumor Regression in Grade I or II	0/2 (0%)	2/4 (50%)	2/2 (100%)

BACKGROUND AND OBJECTIVES

- SV-BR-1-GM is a breast cancer cell line with features of antigen-presenting cells including expression of HLA class II molecules (Lacher et al., Front Immunol. 2018 May 15;9:776)
- Patients who match SV-BR-1-GM at 1 or more HLA alleles may be more likely to respond to treatment based on previous observations.
- **"Monotherapy" Study (WRI-GEV-007):** 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 every 2 weeks x3 then monthly. Prior to SV-BR-1-GM inoculation, a skin test for immediate hypersensitivity is conducted using irradiated SV-BR-1 parent cells or to SV-BR-1-GM (1±0.2 million cells into the forearm).
- **Combination Therapy Study (BRI-ROL-001):** pembrolizumab (200 mg IV) in combination with the regimen from the Monotherapy study with cycles every 3 weeks
- The objectives are to evaluate the safety, preliminary efficacy and pharmacodynamic activity of the SV-BR-1-GM regimen with or without pembrolizumab (KEYTRUDA).

RESULTS

Delayed-Type Hypersensitivity (DTH)

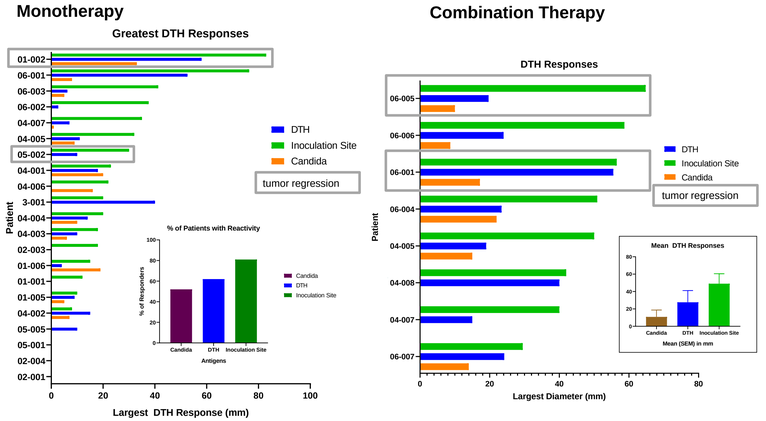


Figure 1. Delayed-type hypersensitivity (DTH). DTH is a good marker of cellular (T cell) immune responses. Candida (positive control) or 1x10^6 irradiated SV-BR-1-GM or parental SV-BR-1 cells were injected intradermally in the forearm ("DTH"). Therapeutically, 5x10^6 SV-BR-1-GM cells were injected per site intradermally, in 4 sites in the upper back and thighs ("Inoculation Site"). 2±1 days later, these sites were assessed for erythema and induration. The largest response (diameter of erythema or induration) for each patient is shown. Means of the DTH values are shown in the insets. **Conclusion: All the patients with follow-up information developed DTH to SV-BR-1/SV-BR-1-GM, despite anergy to Candida in some patients, indicating potent immunogenicity of SV-BR-1/SV-BR-1-GM. The most robust responses were seen in 3 out of 4 patients with objective tumor regression (01-002, 06-005, 06-001).**

RESULTS cont'd

Humoral Responses in the Mono- and Combination Therapy Studies

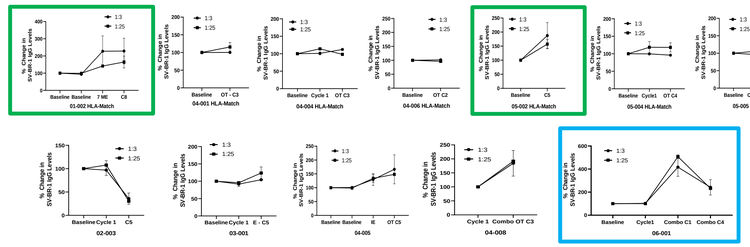


Figure 2. Anti-SV-BR-1 antibody titers in patient sera. SV-BR-1 cells were incubated with 1:3 or 1:25 diluted patient sera then stained with fluorescently labeled anti-human IgG and analyzed by flow cytometry. Both patients with HLA matches (≥ 1 allele; top row) and without (bottom row) developed antibody titer changes. Baseline: before treatment with first dose of SV-BR-1-GM; Cycle 1: Blood draw before treatment (Baseline), ME: Months Evaluation. OT: Off-Treatment, IE: Initial Evaluation; Combo: Combination Therapy (note that subjects 04-005, 04-007, 05-005 and 06-001 rolled over from the monotherapy study). C: cycle number.
Conclusion: IgG responses to SV-BR-1 are elicited following SV-BR-1-GM inoculations. The best responses are seen in those with tumor shrinkage (boxed).

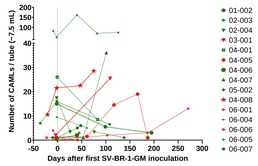
Combination Therapy

	Patient Characteristics – Combination Therapy			
HLA matches	Any (n=11)	None (n=4)	1+ (n=7)	2+ (n=5)
Age	61 ± 9	61 ± 11	61 ± 9	60 ± 11
Median Prior Systemic Regimens	4 (range 1-14)	6 (range 2-10)	4 (range 1-14)	4 (range 1-14)
% ER/PR +	70%	75%	67%	50%
% Her2/neu +	50%	50%	50%	50%
% Triple Negative	0%	0%	0%	0%
% Grade I or II	3/9 (33%)	1/3 (33%)	2/6 (33%)	1/4 (25%)
Tumor Regression	2/11 (18%)	1/4 (25%)	1/7 (14%)	1/5 (20%)
DTH Response	8/10 (80%)	4/4 (100%)	4/6 (67%)	2/4 (50%)
Tumor Regression in DTH Responders	2/8 (25%)	1/4 (25%)	1/4 (25%)	1/2 (50%)
Tumor Regression in Grade I or II	2/3 (67%)	1/1 (100%)	1/2 (50%)	1/1 (100%)

Best Responders:
Patient 06-001: ER+/HER2-, Grade II, Hepatic Metastases, Robust DTH, no HLA Matches, 25% reduction in sum of greatest diameters of target lesions, 13% reduction in all lesions.
Patient 06-005: ER+/HER2-, Grade II, Adrenal and Dural Metastases, Robust DTH, 2 HLA matches with Bria-IMT™, 29% reduction in sum of greatest diameters of target adrenal lesion, 28% reduction in all lesions → Patient transitioned to combination with INCMGA00012 – safe and well tolerated to date; compared with original baseline had a 26% reduction in the sum of greatest diameters of the target adrenal lesion and a 35% reduction in all lesions

Patients with robust DTH (06-001 and 06-005) and Grade II tumors (moderately well differentiated) had a marked reduction in tumor size, suggesting that a robust immune response correlates with tumor regression even without HLA matching. Patients with well- or moderately differentiated tumors appear more likely to respond.

Circulating Cancer associated macrophage-like cells (CAMLs)



Green symbols: Patients with ≥ 1 HLA match to SV-BR-1-GM
Red symbols: Patients without an HLA match

Figure 3. Patients with ≥ 1 HLA match tend to respond to SV-BR-1-GM regimen with decreased CAML* burden.
*Adams et al., Proc Natl Acad Sci USA. 2014 Mar 4;111(9):3514-9

CONCLUSIONS & HYPOTHESES

- **The SV-BR-1-GM regimen +/- PD1 inhibitor is able to induce an effective immune response and tumor regression in advanced breast cancer.**
- **Addition of a PD1 inhibitor can compensate for lack of an HLA match with tumor regression seen in heavily pre-treated metastatic breast cancer.**
- **Patients with Grade I or II tumors, and those able to generate a robust immune response, appear more likely to respond.**