ABSTRACT

BACKGROUND: SV-Br-1-GM is a GM-CSF-engineered breast cancer cell line employed after irradiation—as a targeted immunotherapy for advanced breast cancer. Tumor regressions at metastatic sites have been most notably in patients with HLA allele matches to the cell line. We are assessing SV-Br-1-GM in the Phase IIa portion of a Phase IIIb clinical trial in metastatic and locally recurrent breast cancer (ClinicalTrials.gov identifier NCT03066947). Additionally, we are co-developing a companion diagnostic (BriatImm™) to identify patients likely to respond to SV-Br-1-GM. Currently, BriatImm™ consists of HLA typing; however, we have begun assessing biomarkers in parallel to determine characteristics, circulating (CTCs), and cancer-associated macrophage-like cells (CAMLs) from patients collected at baseline and after inoculation of SV-Br-1-GM to lay additional components to improve accuracy, with the number/subtyping of CTCs and CAMLs being prognostic indicators.

METHODS: Subjects were pre-treated with low dose cyclophosphamide to reduce immune suppression. SV-Br-1-GM is inoculated intradermally with follow-up local injections of FCA2. Cycles are every 2 weeks for 3 months. HLA typing was conducted via LaType R5-00 Kits (One Lambda). Cytokines were measured via single- or multiplex assays. Anti-SV-Br-1 antibodies were determined by incubation of SV-Br-1 cells with diluted patient sera followed by staining with a fluorescently-labeled anti-IgG antibody and detection by flow cytometry. CTCs and CAMLs were evaluated by CellTiter™ at Creative MicroTech.

RESULTS: To date, 16 clinical trial subjects have been inoculated with the SV-Br-1-GM regimen as rescue immunotherapy. All were treatment refractory and had received a median of 4.5 prior chem/biological therapy regimens (range 1-13). Two of the 16 patients remained on study for 3 months (5 cycles) with 4 patients currently on study not having reached the 3-month evaluation time point. Objective regression of tumor was seen in 2 subjects. One subject had virtually complete resolution of 20 of 20 lung metastases noted at 3 and 6 months (but with progressive bone and liver metastases). Another subject had improvement of chest wall metastases and quality of life but expired due to neutropenia related causes. Response appeared to correlate with HLA allele matching to SV-Br-1-GM. Anti-SV-Br-1 antibody titers increased in several patients. Among the cytokines assessed, interleukin (IL) 2 levels increased in HLA-DRB mismatched subjects after SV-Br-1 vaccine patients evaluated, CTCs were present in 6 patients at baseline while CAMLs were present in all 15. Five of 5 patients evaluated for PD 1 expression had mostly low

CONCLUSIONS: In addition to the patients’ HLA types, several pharmacodynamic parameters correlated with tumor regression and/or HLA matching status. CTCs or CAMLs are frequently detectable in this population, and in 6 patients at baseline while CAMLs were present in all 15. Five of 5 patients evaluated for PD 1 expression had mostly low

Cytokine responses to SV-Br-1-GM

SV-Br-1-GM cells express breast cancer epithelial antigens induced by dendritic cells and presented to CD4+ and CD8+ T cells which thereby may attack the patients’ tumors.

SV-Br-1-GM also secretes GM-CSF which supports antigen presentation by dendritic cells.

Circulating Cancer-Associated Macrophage-Like Cells (CAMLs)

CAMLs are giant macrophage-like cells associated with patient tumors and found in the circulation of cancer patients from a variety of cancer types. The presence of tumor markers in CAMLs suggests that CAMLs phagocytose tumor material (Adams et al., 2016). Reduction in CAML frequency and size, and CAML size following treatment may indicate a favorable response. Figure 4A shows that subject with SV-Br-1-GM responded with a reduction in their CAML numbers. CAML numbers were also reduced for 04-02, who had no HLA match to SV-Br-1 and did not respond with worsening regression. Figure 4B suggests that the max. CAML size has less of a predictive value than CAML numbers in our very small study.

Anti-SV-Br-1 Antibody (IgG) titers in patient sera

Table 1. HLA-A,-B,-DRB Alleles of Selected Clinical Trial Subjects. 0A02 was enrolled in a previous Phase I study (Wisman and Cha, 2016); the other subjects in NCI-002-007 (ClinicalTrials.gov identifier NCT03066947). Allele matches to SV-Br-1-GM are highlighted in green while allele group matches are highlighted in gray. (1) HLA-DR 14:01 PM6 was not found to be expressed in SV-Br-1-GM cells. (**) see Figure 3.

SUMMARY

SV-Br-1-GM is a whole-cell targeted immunotherapy for advanced breast cancer: Pharmacodynamic markers of response

SV-Br-1-GM cells (BriatImm™) directly activate CD8+ and CD4+ T cells.

SV-Br-1-GM cells exhibit breast cancer epithelial antigens induced by dendritic cells and presented to CD4+ and CD8+ T cells which thereby may attack the patients’ tumors.

SV-Br-1-GM also secretes GM-CSF which supports antigen presentation by dendritic cells.

REFERENCES

