Response to a modified whole tumor cell targeted immunotherapy in patients with advanced breast cancer correlates with tumor grade

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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 and expressing both HLA-I and II. The patient cell line, SVBR, was derived from a patient with grade II (moderately differentiated) breast cancer. We report molecular characterization of SV- BR-1-GM, noting it retains features of a grade II tumor, and report enhanced disease control in patients with grade I or II breast cancer.

Methods: SV-Br-1 and SVBR-1-GM were characterized molecularly using RNAseq and proteomic analyses. We treated 23 evaluable patients with recurrent and/or metastatic breast cancer refractory to standard therapy. The SV-Br-1-GM regimen included cyclophosphamide 300 mg/m² 2×d to intrapread to intratumoral injection of SV-Br-1-GM cells divided into 6 injections (10 IU/area) about 48 and 96 hours subsequently. Cycles were q6 weeks q3 then q6 m (clinical TCT0306/02). Eleven patients were treated in combination with a PD-1 inhibitor (pembrolizumab or INCMG00012) (clinical TCT03328/02). Disease response was evaluated radiographically q3 mo as clinically indicated.

Results: To estimate the tumor grade represented by the SV-Br-1-GM cell line, we developed a score we refer to as Relative Molecular Grade (RMG). SV-Br-1-GM is most similar to the MDA-MB-468 cell line (RMG = 63) and is closest to the mass spectrometric analysis of BR-141, which was classified as moderately differentiated. Basal carcinoma is less aggressive than Basal II but more aggressive than Luminal, suggesting that SV-Br-1-GM may have retained features of a grade II breast cancer. GRM-1-GM expresses Class I (HLA-A, B, and C) and Class II (HLA-DR and -DP) molecules, and the HLA-DR expression is enhanced by treatment with IFNγ. SV-Br-1-GM expressed 31 genes which are overexpressed in BR-141 breast tumors and 3 genes expressed in breast tissue. In 30 patients treated with the SV-Br-1-GM regimen (10 patients with grade I breast cancer, 4 who began the SV-Br-1-GM regimen vs combination with a PD-1; and 7 with combination therapy alone) there were 7 grade II breast cancer and 1 grade I breast cancer (Table). These patients were heavily pre-treated with an average of 10 prior regimens. While only one patient with grade II breast cancer showed disease control, 75% of the patients with grade I or II tumors showed disease control. Patients remained on study for up to 259 days.

Conclusions: SV-Br-1-GM appears to retain characteristics of a moderately differentiated breast cancer, expresses multiple potential tumor antigens, and can elicit disease control especially in patients with grade I and II breast cancer.

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 9:1577)
- SV-Br-1-GM was derived from a Grade II (moderately differentiated) breast cancer biopsy tumor. SV-Br-1-GM was used in 2 studies:
  - “MonotherapY” Study (RRJ-GE07): The SV-Br-1-GM regimen includes: low dose cyclophosphamide to reduce immune suppression (300 mg/m² 2×d prior to inoculations); 20-40 million live GM-CSF transfected SVBR cells were aminium split into 4 sites; and intradermally divided (10,000 IU/site) into the inoculation sites. 2-4 days later with cycles every 2 weeks x3 then monthly. Prior to SVBR-1-GM inoculation, a skin test for immediate hypersensitivity is conducted using irradiated SVBR-1-GM or to SVBR-1-GM split into the forearm.
  - Combination Therapy Study (RRJ-ROLL-001): pembrolizumab or INCMG00012 (200 mg IV) in combination with the monotherapy from the RRJ-GE07 study cycles every 3 weeks.
  - Here we characterize the SV-Br-1-GM cell line molecularly and evaluate the clinical response in patients with Grade I or Grade II tumors.

RESULTS

Molecular Characterization of SV-1-GM


Figure 2. Progression free survival by study. Overall Survival

Figure 3. Baseline characteristics. Progression free survival (PFS) was collected on all patients, and overall survival (OS) in 174 patients. CONCLUSIONS AND HYPOTHESES

- The patients with grade III tumors in our studies were very heavily pre-treated with a median of 7 prior systemic therapies; disease control was observed in patients treated with the SV-Br-1-GM regimen (75% DTH response and 75% disease control in DTH responders).
- The SV-Br-1-GM regimen +/- PD1 inhibitor can induce an effective immune response and tumor regression in heavily pre-treated advanced breast cancer, especially patients with grade II tumors.
- PD1 and OS in this heavily pre-treated group compare well with 3rd line or metastatic breast cancer, 1st line or SBR-Br-1-GM regimen or to SV-Br-1-GM split into the forearm.

REFERENCES