Personalized off-the-shelf whole cell immunotherapy for cancer

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Abstract

SV-BR-1-GM is a GM-CSF secreting breast cancer cell line that also expresses HLA class I & II antigens. SV-BR-1-GM has been demonstrated to possess functional antigen presenting cell activity and is able to directly stimulate CD4+ T cell clones. SV-BR-1-GM was initially derived from a grade II (moderately differentiated) breast cancer metastases and molecular characterization shows it matches most closely with other cell lines derived from grade I or II breast cancers. Irradiated SV-BR-1-GM has been used in a regimen including pre-dose low-dose cyclophosphamide, to reduce immune suppression, and post-dose local IFN-α2b to boost the type 1 response. The SV-BR-1-GM regimen has been used alone ("monotherapy", ClinicalTrials.gov NCT03066947) and in combination with checkpoint inhibitors ("combination", ClinicalTrials.gov NCT03328026).

In the combined monotherapy experience, 26 patients with refractory advanced metastatic breast cancer and one with ovarian cancer were treated with the SV-BR-1-GM regimen with cycles every 2 weeks x3 and then monthly. The combination study uses the SV-BR-1-GM regimen with PD-1 inhibitors pembrolizumab or INCMGA00012 with cycles every 3 weeks (12 patients dosed to date). Four patients crossed over from the monotherapy to the combination study. Analyses include tumor response, progression-free survival, overall survival, circulating tumor cells (CTCs), cancer-associated macrophage-like cells (CAMLs), tumor grade, HLA-type, and the ability to develop delayed-type hypersensitivity (DTH).

The monotherapy patients were heavily pre-treated (median of 4 prior systemic therapies not including hormonal therapy). Disease control (including stable disease (SD), partial (PR) or complete responses (CR)) was seen in 8 patients (30%). 21 patients (78%) developed measurable DTH. Disease control was more frequent in patients who developed DTH (38%), had 2 or more HLA matches with SV-BR-1-GM (67%) and those with grade I/II tumors (63%). In the combination therapy study, disease control was seen in 4 patients (25%) and 9 (82%) developed DTH. Patients with grade I or grade II tumors were more likely to achieve disease control (3/4, 75%) compared with those with grade III tumors (1/8, 13%). In combination with a PD-1 inhibitor HLA matching was not associated with higher response rates. None of the 3 patients with high levels of CTCs at baseline had disease control. Mean and median PD-L1 expression levels on CTCs and CAMLs were higher for patients with grade III tumors compared with grade I/II tumors, but this was not clearly correlated with clinical response. Given the correlation between response and HLA matching in the monotherapy setting, the SV-BR-1-GM cell line is being genetically engineered to express 15 different HLA types in 4 cell lines that can be used to personalize this therapy to patients based on HLA matching. These cells will be pre-manufactured and frozen after irradiation for rapid use in patients based on their HLA type.

In conclusion, the SV-BR-1-GM regimen can produce clinical benefit in very heavily pretreated patients with aMBC refractory to conventional therapies especially if the patients have an intact immune system (DTH), do not have high level of CTCs, have grade I or II disease, and have HLA matching with the SV-BR-1-GM cell line. These insights have been used to design a personalized off-the-shelf immunotherapy for cancer.

Introduction

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)

SV-BR-1-GM was derived from a Grade II (moderately differentiated) breast cancer biopsy. It was stably transfected with the CSF2 gene encoding GM-CSF. SV-BR-1-GM has been shown to act as an antigen-presenting cell, directly stimulating CD4+ T cells in an antigen-specific HLA-restricted manner.

Methods and Materials

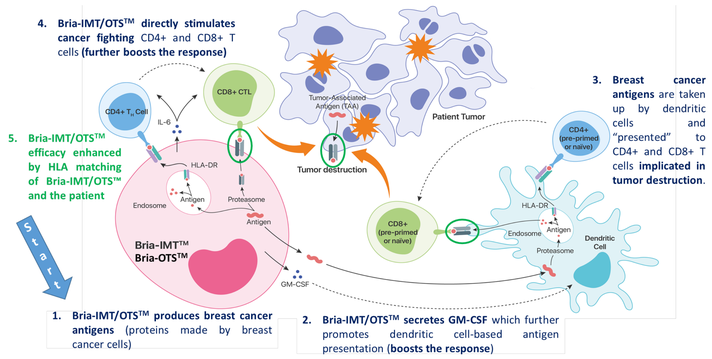
SV-BR-1-GM was used in 2 clinical paradigms:

"Monotherapy": 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 in 4 sites;
- interferon-α2b (10,000 IU x 4) into the inoculation sites ~2 & ~4 days later.
- Cycles every were 2 weeks x3 then monthly.

Combination Therapy with PD-1 Inhibitors: pembrolizumab (200 mg IV) or INCMGA00012 (375 mg IV) in combination with the monotherapy regimen with cycles every 3 weeks.

Figure 1. Mechanism of Action of SV-BR-1-GM.



Results

Monotherapy Experience

- The monotherapy patients were heavily pre-treated (median of 4 prior systemic therapies not including hormonal therapy). Patient characteristics are shown in Table 1.
- Disease control (including stable disease (SD), partial (PR) or complete responses (CR)) was seen in 8 patients (30%).
- 21 patients (78%) developed measurable DTH. Disease control was more frequent in patients who developed DTH (38%), had 2 or more HLA matches with SV-BR-1-GM (67%) and those with grade I/II tumors (63%).

PD-1i Combination Experience

- In the combination therapy study, disease control was seen in 4 patients (25%) and 9 (82%) developed DTH.
- Patients with grade I or grade II tumors were more likely to achieve disease control (3/4, 75%) compared with those with grade III tumors (1/8, 13%).

Table 1. Characteristics of Patients Treated with the Monotherapy Regimen

Patient Characteristics	No HLA Allele Matches (n=7)	1+ HLA Allele Matches (n=20)	2+ HLA Allele Matches (n=6)	All Patients (n=27)
Age	54 ± 15	60 ± 10	60 ± 15	58 ± 12
Prior Regimens	7 (range 2-9)	4 (range 0-12)	5 (range 1-10)	5 (range 0-12)
% ER/PR +	67%	47%	80%	52%
% Her2/neu +	14%	16%	0%	15%
% Triple Negative	33%	37%	20%	36%
Disease Control	29%	30%	67%	30%
Grade I/II	100% (2/2)	50% (3/6)	100% (3/3)	63% (5/8)
Responders (PR)	0% (0/6)	5% (1/20)	17% (1/6)	4% (1/27)

Table 2. Characteristics of Patients Treated with the PD-1i Combination Regimen

Patient Characteristics	No HLA Allele Matches (n=4)	1+ HLA Allele Matches (n=8)	2+ HLA Allele Matches (n=6)	All Patients (n=12)
Age	61 ± 11	60 ± 10	60 ± 11	61 ± 10
Prior Regimens	7 (range 2-9)	5 (range 1-10)	4 (range 1-10)	6 (range 1-10)
% ER/PR +	75%	75%	67%	75%
% Her2/neu +	0%	25%	17%	17%
% Triple Negative	25%	25%	33%	25%
Disease Control	25%	38%	33%	33%
Grade I/II	1/1	2/3	1/2	3/4
Responders (PR)	0% (0/4)	13% (1/8)	17% (1/6)	8% (1/12)

Table 3. Characteristics of Grade I/II Patients Treated with Either Regimen

Patient Characteristics	No HLA Allele Matches (n=2)	1+ HLA Allele Matches (n=9)	2+ HLA Allele Matches (n=5)	All Patients (n=11)
Age	57 ± 22	59 ± 12	57 ± 16	58 ± 13
Prior Regimens	9	7	7	8
% ER/PR +	100%	78%	100%	82%
% Her2/neu +	0%	33%	20%	27%
% Triple Negative	0%	11%	0%	9%
Disease Control	100%	56%	80%	64%
Responders (PR)	0% (0/2)	22% (2/9)	40% (2/5)	18% (2/11)

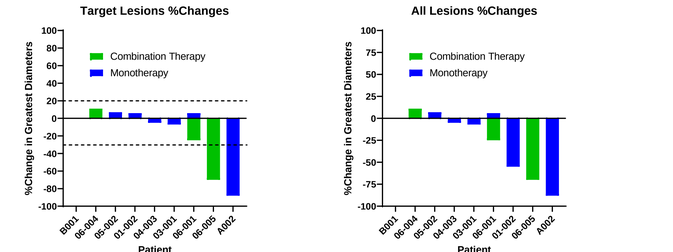


Figure 2. Lesion Size Changes. There were 9 patients with grade I/II tumors with imaging both before and after treatment. The % change of the sum of greatest diameters of their tumors is shown for A) Target lesions and B) All lesions.
Conclusion: The SV-BR-1-GM regimen can elicit marked tumor reduction especially in patients with Grade I/II tumors.

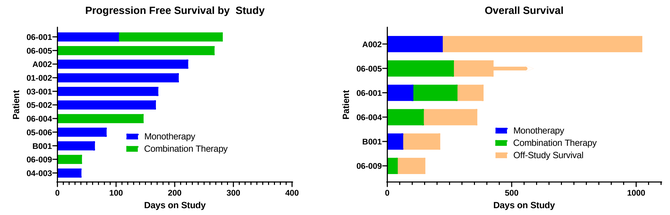


Figure 3. Survival Data. Progression-free survival (PFS) was collected on all patients, and overall survival (OS) on 6 patients.
Conclusion: In spite of having failed multiple prior treatment regimens, the SV-BR-1-GM regimen can result in protracted progression-free survival and overall survival especially in patients with Grade I/II tumors

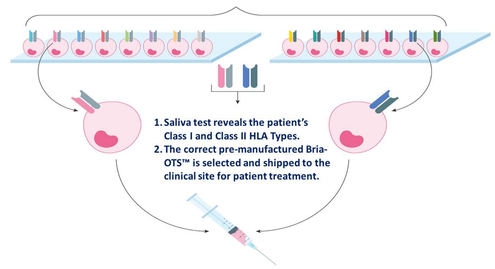


Figure 4. Future Directions. Development of a personalized off-the-shelf immunotherapy. Given the enhanced response rate in patients who match SV-BR-1-GM and 2+ HLA types for monotherapy, SV-BR-1-GM has been genetically engineered to express multiple HLA types, including 8 Class I and 7 Class II HLA types, which will allow a single HLA match with >99% of the population and a double match in ~90%.
Prospects: This personalized off-the-shelf approach to immunotherapy is planned to enter the clinic in late 2021.

Discussion and Conclusions

Cancer immunotherapy shows great promise in the development of novel approaches with fewer side-effects than chemotherapy and biological therapies. However, the current immunotherapies have limited efficacy and can cause autoimmune disease.

SV-BR-1-GM has a unique mechanism of action, acting both as a source of breast cancer antigens and able to function as an antigen presenting cell, thereby boosting the immune response. This is in part dependent on HLA matching between the patient and the cell line. The SV-BR-1-GM regimen appears capable of eliciting disease control and clinical benefit in patients with advanced breast cancer, especially those who match at 2+ HLA alleles and those with Grade I/II tumors (from which SV-BR-1-GM was derived).

Capitalizing these observations, SV-BR-1-GM has been genetically engineered to express 8 Class I and 7 Class II HLA alleles, which will allow a single HLA match with >99% of the population and a double match in ~90%. These cell lines will provide a personalized approach to cancer immunotherapy that is off-the-shelf, eliminating the complex manufacturing logistics of other personalized immunotherapies.

Contact

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