Decreases in Circulating Tumor Associated Cells Predict PFS and OS in a Pooled Analysis of Phase I Clinical Trials Using SV-BR-1-GM Therapy with or without Immune Check-Point Inhibitors in Metastatic Breast Cancer Patients

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San Antonio Breast Cancer Symposium
December 6-10, 2022
Poster ID: P1-05-28

BACKGROUND

In metastatic Breast Cancer (mBC), Circulating Tumor Cells (CTCs) are clinical indicators of worse prognosis and patients (pts) not responding to current therapy. However, CTCs are rare, found in <20% of mBC pts, and many pts without CTCs may also progress. Recently an antigen presenting pro-tumorigenic macrophage (Cancer Associated Macrophage-Like cell [CAML]) was identified in the blood, found in >90% of mBC pts, and appears to indicate tumor response to new therapies[1].

SV-BR-1-GM is a mBC cell line (**Figure 1**) with antigen presenting characteristics that was developed for treating mBC[2,3]. SV-BR-1-GM is given in combination with low dose cyclophosphamide to reduce immune suppression, and local interferon alpha to boost the response. This regimen is given as a monotherapy (monoTx), or in combination with PD-1 checkpoint inhibitors (comboTx).

We report post-hoc results of a pooled analysis of n=18 monoTx mBC pts and interim results of n=21 comboTx (with an additional 4 pts that rolled from monoTx to comboTx) to analyze the predictive value of CTCs & CAMLs, as well as CAML PD-L1 expression, isolated from pt peripheral blood pre & post treatment to predict Progression Free Survival (PFS) and Overall Survival (OS) at 24 months.

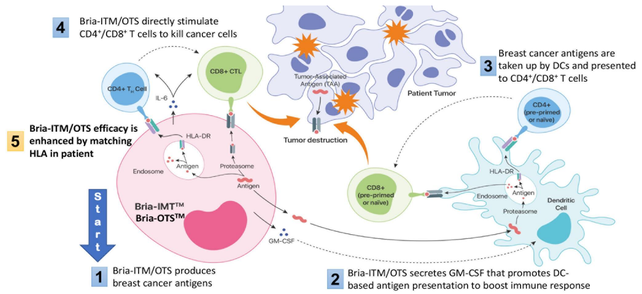

Figure 1. Dual mechanism of action. *SV-BR-1-GM cells secret GM-CSF that supports presentation of breast cancer antigens by Dendritic Cells (DCs). SV-BR-1-GM also directly presents antigens to CD4+ and CD8+ T cells.*

MATERIALS AND METHODS

The SV-BR-1-GM regimen includes low pre-dose cyclophosphamide, intradermal inoculation of ~20 million irradiated SV-BR-1-GM cells and post-dose local interferon-α with cycles every 2 weeks x 3, then monthly. ComboTx adds an anti-PD-1 antibody with cycles every 3 weeks. Blinded blood samples were taken at baseline (BL), prior to starting SV-BR-1-GM therapy (n=39), and a 2nd sample (T1) taken after therapy initiation (~52 days) obtained as part of the exploratory portion of 2 prospective phase I/II clinical studies, NCT03066947 & NCT03328026, to evaluate the predictive value of CTCs/CAMLs and CAML PD-L1 measured either high or low as previously described by LifeTracDx® liquid biopsy[3]. The quantities of CTCs & CAMLs were analyzed based on PFS using RECIST v1.1 and OS hazard ratios (HRs) by censored univariate analysis at 24 months.

RESULTS

- CTCs were found in 38% (n=15/39) and CAMLs in 95% (n=37/39). (**Table 1**)
- N=39 mBC pts had BL samples from monoTx or comboTx.
- BL CTCs predicted worse OS (HR=5.2, p=0.0398), but not PFS.
- T1 samples were available from 54% (n=21/39) pts.
- Drop in CTCs/CAMLs after SV-BR-1-GM therapy was seen in 67% of pts, correlating with better PFS HR=11.9, p=0.0012. (**Figure 2**)
- Drop in CTCs/CAMLs after SV-BR-1-GM Tx had a ~460% increase in mPFS (1.8 mo vs 8.3 mo) and ~170% increase in mOS (7.1 mo vs 12.0 mo).
- Drop in CTCs/CAMLs correlated to better PFS (HR 20.6, p=0.0096) in the monoTx group and in the comboTx group (HR 12.1, p=0.0031).
- CAML PD-L1 at BL was correlated with significantly better OS HR=13.8, p=0.0037, consistent with long term benefit of SV-BR-1-GM therapy.

Figure 2. PFS Based on Changes in CTCs/CAMLs

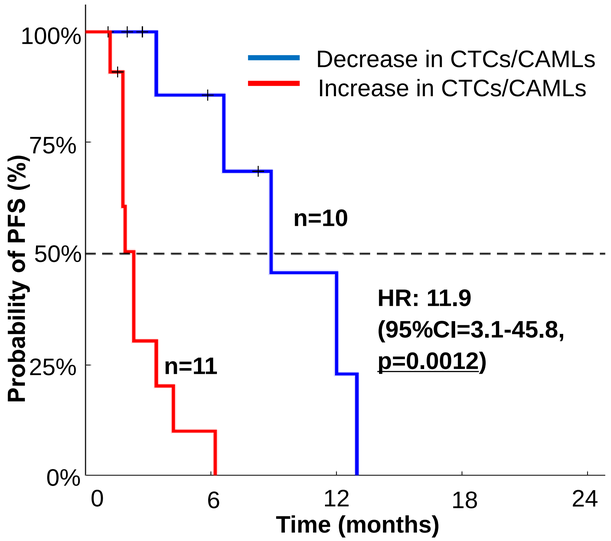

Table 1. Hazard ratio comparisons of CTCs/CAMLs after SV-BR-1-GM Therapy

HR (95%CI) p value	Total 0 vs ≥1 CTCs BL	Total High vs Low CAML PD-L1 BL	Total ↑ vs ↓ CTCs/CAMLs	MonoTx ↑ vs ↓ CTCs/CAMLs	ComboTx ↑ vs ↓ CTCs/CAMLs
n value	24 vs 15	14 vs 25	11 vs 10	5 vs 6	8 vs 6
PFS	0.7 (0.3-1.7) p=0.5916	0.9 (0.4-2.2) p=0.9631	**11.9 (3.1-45.8) p=0.0012**	**20.6 (3.0-141.1) p=0.0096**	**12.1 (2.8-52.7) p=0.0031**
OS	**5.2 (1.3-20.0) p=0.0398**	**13.8 (2.9-65.7) p=0.0037**	2.7 (0.4-13.5) p=0.6106	20.1 (0.3-1284.1) p=0.7237	2.0 (0.4-11.0) p=0.7344

CONCLUSIONS

- CAMLs and/or CTCs were observed in 100% of the pt population.
- Treatment with SV-BR-1-GM regimen was associated with decreases in the presence of CTCs or CAMLs in 67% of pts, correlating with ~460% better mPFS and ~170% better mOS within 2 years.
- SV-BR-1-GM therapy alone, or in combination with anti-PD-1, appears to improve long term clinical outcomes in heavily pre-treated mBC patients.

References

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