Bria-IMT CD8+ Tumor Infiltrating Lymphocytes Turn “Cold” Tumor “Hot” in Metastatic Breast Cancer

Ephraim Parent, MD[1], Carmen Calfa, MD[2], Saranya Chumsri, MD[1], Blaise Bayer, MD[3], Tamar Aghajanian, Pharm D[3], Giuseppe Del Priore, MD[3], William Williams, MD[3], Russ Kuker, MD[2]

[1]Mayo Clinic, Jacksonville, FL, [2]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL [2], [3]BriaCell Therapeutics Corp., Philadelphia, PA

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BACKGROUND

Transforming "cold" tumors into "hot" ones is critical for the success of immuno-oncology therapies, but there has been little evidence that “cold” tumors can be turned “hot”. SV-BR-1-GM, an allogenic human cancer cell line (Bria-IMT) with antigen-presenting capabilities, is designed to counteract the immunosuppressive tumor microenvironment. Zr-89 crefmirlimab berdoxam is a radio-labeled truncated mini-antibody specific to human CD8α developed for CD8 ImmunoPET imaging. We conducted CD8 imaging before and after Bria-IMT treatment to evaluate baseline and subsequent intra-lesional changes in CD8+ T cell tumor infiltration. We now present additional data from the nested feasibility trial of immunoPET in late state MBC.

METHODS

Nested feasibility trial of subjects from two CD8 immunoPET capable tertiary care sites participating in NCT03328026 a randomized phase 2 of Bria-IMT in combination with a check point inhibitor (CPI). Standard Uptake Value (SUV) was evaluated pre-dose and following therapy. Treatment was with the Bria-IMT regimen (cyclophosphamide 300 mg/m^2 2 days prior to SV-BR-1-GM 20 million cells ID in 4 inoculation sites followed by pegylated IFNα 0.1 mcg per inoculation site) in combination with the immune checkpoint inhibitor (CPI) anti-PD-1 antibody retifanlimab 375 mg IV with cycles every 3 weeks.

RESULTS

Table 1: Patient Demographics

N	Age, Median (Range)	BMI, Median (Range)	Prior Systemic Tx Median (Range)
6	60.5, (44-66)	29.3, (26 – 31)	7, (4-8)

Table 2: Summary of Tumor Assessment with SV-BR-1-GM by biomarkers

Biomarkers	Individual Subject#	Best CBR [CR, PR, SD]	CPI Sequence Arm	HLA Match Status
HER2+	11-018	PR	Cycle 1	0
HR + / HER2 -	11-016	SD	Cycle 2	2
	11-017	SD	Cycle 2	3
	15-005	SD	Cycle 2	2
TNBC	11-007	PD	Cycle 2	2
	15-006	PD	Cycle 1	0

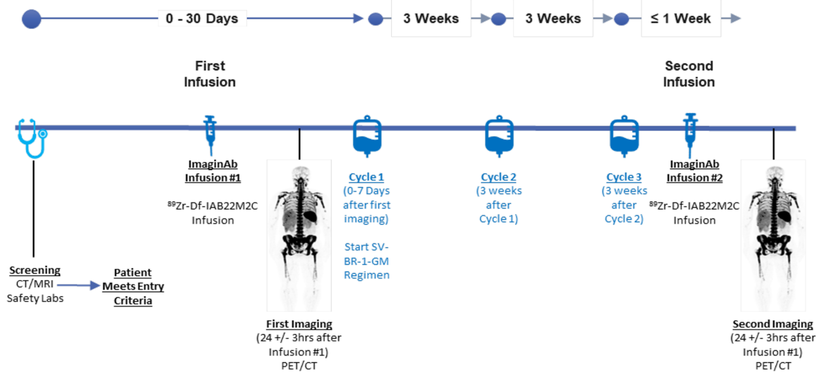
Conclusion: A clinical benefit rate of 67% and an overall response rate of 17% were seen in the CD8+ evaluable patients, including those with HER2+, HR+ and HER2- disease.

Table 3: Summary of Adverse Events (AEs)

Adverse Event	Total	Events	
	Highest Toxicity Grade	Total	Total Related
Injection Site Reaction	1	6	**6**
Nausea	2	5	**2**
Diarrhea	1	3	**0**
Fatigue	2	3	**3**
Vomiting	2	3	**2**
Cough	1	2	**0**
Increased AST and ALT	2	1	**0**
Myalgia	1	2	**2**
TSH Increased	1	2	**2**
aPTT prolonged	1	1	**0**
Allergic reaction to IV contrast	3	1	**0**

Conclusion: The Bria-IMT regimen with CPI was generally well tolerated.

6 patients enrolled in the completed randomized phase 2 Bria-IMT trial with advanced heavily pretreated MBC also had pre- and post-treatment CD8 PET scans. Prior lines included antibody-drug conjugates (ADCs) and CPIs. All patients had progressed on prior treatment. Four of these patients were randomized to start the CPI after 2 cycles of Bria-IMT to “train” the host immune system before adding the CPI; 2 patients were randomized to begin CPI concurrent in C1 with Bria-IMT (11-018, and 15-006). Four patients matched at least 2 SV-BR-1-GM HLA loci, which in previous publications of the Bria-IMT regimen alone is associated with greater clinical benefit. On follow-up CD8 ImmunoPET, each patient demonstrated an increase in SUV in at least one metastatic lesion (range –57.4 to +442.9%) including lung, soft tissue, liver, lymph node, dural based and bony metastases. There was no consistent change recognized in any of these groups except as noted below. Evaluable subjects with HLA matches (3/4) did not experience any increases in CD8+ ImmunoPET SUV at inguinal lymphatic sites while those without HLA matches (n=2) showed increase in CD8 SUV at these sites. In addition, bilateral axillary lymph nodes presented with a median SUV of 6.4 (1.4 - 15.1) after treatment as compared to a median SUV of 7.4 (2.1-18.9) at baseline. 3 out of the 6 patients showed a decrease in neutrophil/lymphocyte ratio NLR at cycle 2 when compared to baseline values. The longest survivor (11-018) on trial (>1yr, after 6 prior lines, ER/PR +, HER2+) CD8 PET also had the largest percentage (442.9%) increase of any patient in SUV (right frontal dural based). This lesion completely resolved around cycle 8.



Abbreviations: CT = computed tomography; hrs = hours; IOT = immuno-oncology therapy; MRI = magnetic resonance imaging; PET = positron emission tomography.

Figure 1: Anti CD8+ Immuno PET imaging schema for patients who opted into the corollary study of Phase 2 trial.

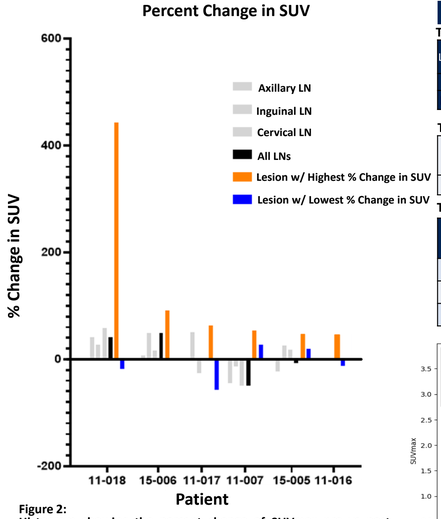


Figure 2:
Histogram showing the percent change of SUVmax pre vs post treatment.

Best Responder (Patient 11-018) Changes in SUV

Table 4A: Absolute Change in SUV Pre vs Post Tx

Location	Inguinal node	Axillary node	Cervical node	Median LN	Highest Change	Lowest Change
PreTx	2.2	2.2	2.2	2.2	0.7	1.1
PostTx	3.1	2.8	3.5	3.1	3.8	0.9

Table 4B: Percent Change in SUV Pre vs Post Tx

Inguinal LN	Axillary LN	Cervical LN	All LNs	Highest % Change	Lowest % Change
+40.9%	+27.3%	+59.1%	+40.9%	**+442.9%**	-18.2%

Table 5: Absolute Change in cancer antigens from baseline to cycle 9.

Tumor Marker	Before Bria-IMT (U/mL)	After 9 Cycles of Bria-IMT (U/mL)
CEA	5.1	1.5
CA 27.29	209.2	29.1
CA 15-3	199.4	32.9

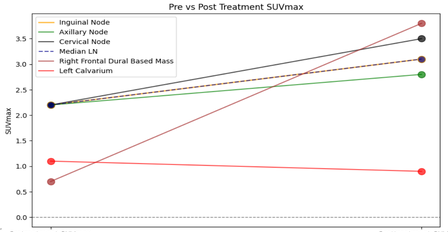


Figure 3: Spider-plot showing absolute change in SUVmax in patient 11-018.

IMAGING

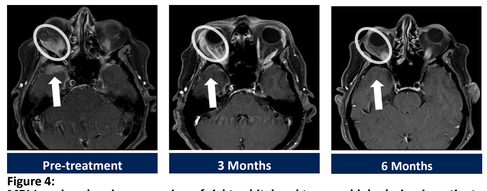
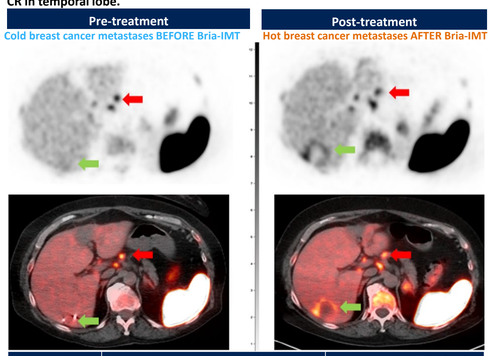


Figure 4:
MRI Imaging showing regression of right orbital and temporal lobe lesion in patient 11-018. 3 month imagining showed uncertain changes in periorbital lesion but near CR in temporal lobe.



Tumor Marker	Before Bria-IMT (U/mL)	After Bria-IMT (U/mL)
CEA	2.0	1.4
CA 27.29	34.0	Not Available
CA 15-3	17.0	9.7

Figure 6A: Transaxial Zr-89 and fused PET/CT of patient 11-007 showing subtle increased 89Zr-CD8 uptake in the segment 7 lesion indicated by fiducial markers (green arrow). Venous T1+contrast MRI of the liver shows unchanged size of the segment 7 lesion compared to prior MRI (not shown). Incidentally noted small physiologic mesenteric and portahepatis lymph nodes (red arrow).

Figure 6B: Transaxial Zr-89 PET and fused PET/CT of patient 11-007 show new pronounced accumulation after vaccination with new area seen on MRI (green arrow).

Conclusion: Bria-IMT combination therapy is able to induce CD8+ T cell infiltration into metastatic breast cancer tumors.

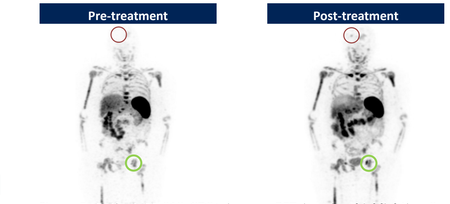


Figure 5: Patient 11-018 CD8+ immunoPET imaging highlighting 2 areas of increased uptake post treatment (right frontal dural based, left inguinal lymph nodes)

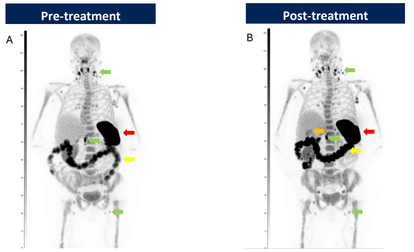


Figure 7A: Patient 15-006 (PD), 64 year old woman with MBC s/p several round of systemic and targeted therapy; known hepatic metastases previously treated with Y-90 radioembolization and thermal ablation. Maximum intensity images (MIP) of Zr-89 CD8+ cells shows typical physiologic distribution in spleen (red arrow) and lymph nodes (green arrow). Heterogeneously intense 89Zr-CD8 uptake in the marrow and liver. 89Zr-CD8 uptake in the colon without known significance (yellow arrow).

Figure 7B: Patient 15-006, repeat Zr-89 PET after vaccine administration demonstrates new "hot" focal uptake in the patient with known hepatic metastatic deposit (orange arrow). Additionally, there is interval increased uptake in majority of benign lymph nodes and relatively stable uptake in the normal liver, bone marrow, and blood pool.

For ongoing phase 2 study on similar patients, please refer to additional poster: **Chumsri et al SABC 2024 PS3-06:** "Overall Survival Results of BRIA-IMT Allogenic Whole Cell-Based Cancer Vaccine”

CONCLUSION

We report additional data supporting the hypothesis that "cold" tumors can become "hot" when treated with Bria-IMT in combination with an anti-PD-1 CPI, as demonstrated by metastatic site-specific CD8+ PET results. Subjects in a now nearly completed randomized phase 2 demonstrated responses of metastatic lesions on CD8 ImmunoPET. The nonspecific nodal localization of CD8 ImmunoPET may indicate a systemic activation of CD8 positive lymphoid cells in response to peripheral non-lesional SV-BR-1-GM injections. These results suggest a potential value of CD8 ImmunoPET in identifying lesions that are progressing on treatment versus pseudo progression. It also provides support that the Bria-IMT combination immune-based therapy can result in an increase of CD8+ tumor infiltrating lymphocytes in breast cancer metastatic sites as well as in lymphoid organs. This advance may aid in triaging patients, adjudicating pseudo-progression and predicting clinical benefit of immune based therapies.