CD8+ Tumor Infiltrating Lymphocytes Turn a Cold Tumor Hot in Metastatic Breast Cancer

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Purpose/Background

Turning “cold” tumors “hot” is considered essential for immune-oncology therapies to be effective. SV-BR-1-GM is an allogenic human cancer cell line with antigen presenting cell activity designed to overcome the immune suppressive tumor microenvironment when given with Cytoxan and interferon (the Bria-IMT regimen). However, until now there has not been proof that “cold” tumors can become “hot” with this therapy. Using Zr-89 crefmirlimab berdoxam, a zirconium-89 labelled minibody (ImaginAb, Inc) specific to human CD8α and developed for CD8 ImmunoPET, we image before Bria-IMT administration and after 3 cycles to assess the baseline status as well as changes in CD8 cell presence after initiation of therapy. Here we present the first evidence that immunologically cold tumors can become hot on treatment with Bria-IMT combined with an anti-PD-1 checkpoint inhibitor (CPI), showing CD8+ cells increased over baseline using CD8 ImmunoPET.

Case

After informed consent, a 61 year-old Hispanic female, enrolled in the ongoing randomized phase 2 of Bria-IMT trial in advanced heavily pretreated metastatic breast cancer (MBC) (NCT03328026). Her history included MBC in May 2020, ductal type, grade 3, triple negative breast cancer (TNBC) with 6 prior lines of therapy including a Trop-2-directed antibody-drug conjugate and 6 lines of chemotherapy. Precision medicine testing identified no actionable targets. All prior therapies had progressive disease as their best response. The subject was randomized to start the CPI after 2 cycles of Bria-IMT to “train” the host immune system before proceeding with combination immune-oncology therapy. Baseline testing revealed the subject to be anergic to candida and SV-BR-1-GM inoculation. However, by cycle 3 delayed-type hypersensitivity to SV-BR-1GM developed. Interestingly the subject matched SV-BR-1-GM at 2 HLA loci: DRB3*02:02 and DRB1*11:04 which in previous publications is associated with greater clinical benefit. Tumor markers were stable or decreased slightly including CEA (25% decrease) and CA 15-3 (43% decrease). Circulating Tumor Cells (CTCs) and Cancer Associated Macrophage Like cells (CAMLs) also improved. Standard imaging at baseline showed 3 main sites of disease including a large right breast mass, multiple right axillary lymph nodes and a right lower lobe mass with CD8 ImmunoPET uptake in these areas similar to the blood pool. On the follow-up CT imaging, all of these lesions increased in size with newly appreciated pulmonary nodules. The right lower lobe mass showed increased CD8 ImmunoPET accumulation with an SUV of 5.8 (close to the liver background) as compared to an SUV of 2.2 at baseline. The lesions in the right breast and right axilla remained at blood pool levels. There was an increase in CD8 ImmunoPET uptake in bilateral inguinal lymph nodes reaching an SUV of 4.8 as compared to SUV 2.2 at baseline. In addition, there were non-enlarged lymph nodes in bilateral axillary regions that also showed increased radio-tracer accumulation reaching an SUV of 9.5 as compared to SUV 4.9 at baseline. Of note, after the initial submission of the abstract, two additional patients were imaged, which are shown in Figure 2 and Figure 3.

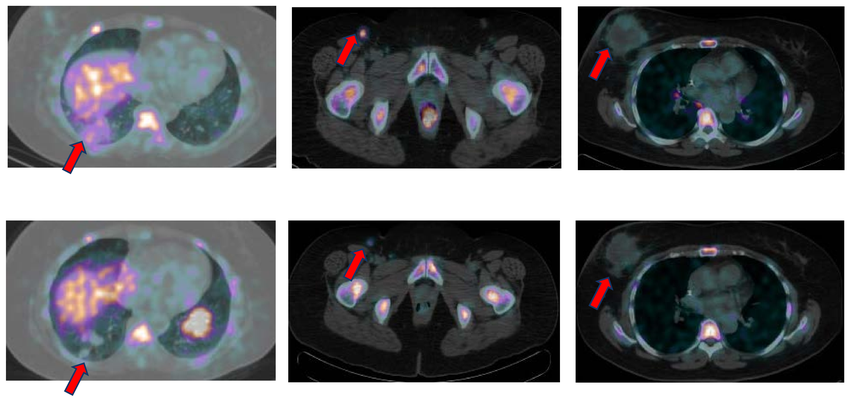

Figure 1 illustrates follow-up scans (top) and baseline scans (bottom). Patient had increased CD8 tracer uptake in the right lower lobe nodule (SUV max percent change 163%) and right inguinal lymph nodes (SUV max percent change 80%). There was no significant change in the right breast mass, other than mild anterior increased CD8 tracer uptake. Overall, there was heterogenous intra-patient distribution, in which some lesions demonstrated CD8+ cell infiltration, while others, such as the right-sided breast mass, did not. This raised the possibility of pseudo-progression, but subsequent CT images (not shown) demonstrated growth of all lesions. Patient is currently no longer in the clinical trial.

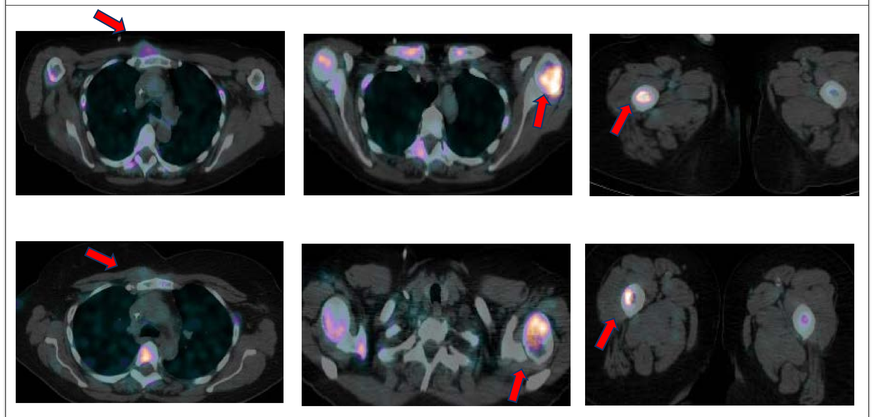

Figure 2 demonstrates follow-up scans (top) and baseline scans (bottom). Patient had extensive bone disease, which is difficult to evaluate on PET scan because CD8+ cells infiltrate the bone marrow. Patient did demonstrate increased CD8+ cell uptake in the sternal soft tissue mass (SUV max percent change +82%), left proximal humerus (SUV max percent change +71%) and right proximal femur (SUV max percent change +23%). No apparent significant change on the contralateral femur or humerus. Patient did not have significant nodal uptake. Patient is currently still on trial with radiographic stability.

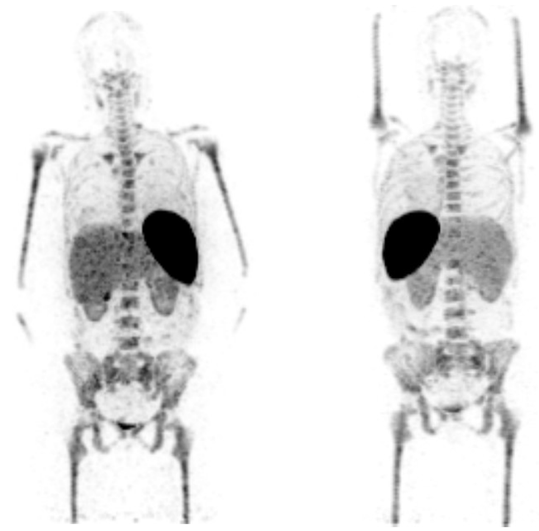

Figure 3 demonstrates follow-up scan (left) and baseline (right). This patient demonstrated liver and omental disease, as well as multifocal osseous metastatic disease. There was no significant percent SUV max change between the baseline and follow-up scan with physiological accumulation of the CD8 agent in mainly the spleen, liver, bone marrow and kidneys. One possible explanation is that these lesions were not metabolically active, and, as a result, there was no treatment induced influx of CD8+ cells. A follow-up FDG PET would have been beneficial to assess for any viable lesions. Overall, patient progressed in her disease with new ascites. Furthermore, the patient’s molecular profile changed so a new treatment plan is currently being pursued. Patient is no longer within the clinical trial.

Conclusion

Patient in Figure 1 demonstrated a mixed response of metastatic lesions on CD8 ImmunoPET with encouraging changes in peripheral blood tumor markers and CTCs. The nonspecific nodal localization of CD8 ImmunoPET may indicate a systemic activation of CD8 positive lymphoid cells. This shows the value of CD8 ImmunoPET in identifying lesions that are progressing on treatment versus pseudo progression as well as the ability to visualize intra-patient and intra-lesion heterogeneity. It also provides support that the Bria-IMT + CPI combination immune-based therapy can result in an increase of CD8+ tumor infiltrating lymphocytes in breast cancer metastatic sites as well as an increase in lymphoid organs. This advance may aid in triaging patients, adjudicating pseudo-progression and predicting clinical benefit of immune based therapies.