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Preliminary immune correlatives from BCA101 trial show favorable modulation of tumor immune microenvironment

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Background: BCA101 is a bifunctional fusion antibody targeting EGFR and TGF-β. TGF-β pathway activation is a hallmark of human immune-excluded tumors, and TGF-β expression is associated with resistance to anti-PD-1 blockade. Neutralization of TGF-β removes an immunosuppressive signal that drives accumulation and polarization of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) in solid tumors, while EGFR inhibition targets tumor cell-intrinsic oncogenic signaling. Co-targeting of EGFR and TGF-β locally directly impacts tumor progression while enhancing the immunogenicity of tumors.

Methods: Patients with multiple solid tumor types, including colorectal cancer, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, and squamous non-small cell lung cancer (SqNSCLC) were treated with escalating doses of either BCA101 alone or in combination with anti-PD-1 (pembrolizumab) enrolled on NCT04429542 trial. We analyzed a variety of proximal signal transduction endpoints and distal tumor, stromal, and/or immune correlatives on pre- and on-treatment tumor biopsies, including Nanostring-based transcriptomic profiling and multiplexed and mass spectrometry-based imaging, as well as multiparametric flow cytometric profiling of circulating PBMCs.

Results: Circulating HLA-DR**-** monocytes were significantly decreased in on-treatment PBMC samples relative to screening. Pathway analysis of on-treatment tumor biopsies revealed enhanced costimulatory signaling, cytokine and chemokine signaling, immune infiltration, and interferon signaling. Top differentially regulated genes in on-treatment biopsies included CCL21, CXCL9, CXCL11, and CXCL13, which are known to recruit T and NK cells. HDAC11, which negative regulates type-I interferon signaling, was significantly reduced in on-treatment biopsies. Notably, two patients with EGFR-amplified SqNSCLC, who both progressed on first-line immunotherapy treatment, were treated with BCA101 at 1250 mg and 1500 mg qw and achieved a partial response (ongoing for 10 months at the time of the data cutoff) and a prolonged stable disease for 11 months, respectively. They exhibited increased CD8+ T-cell infiltration and a reduction in TAMs following treatment.

Figure 1. BCA101-induced transcriptomic changes in the tumor immune microenvironment. Nanostring analysis reveals on-treatment increase in immunogenicity was observed. (**A,B**) Upregulated pathways included: lymphoid compartment, immune cell adhesion and migration, costimulatory signaling, and interferon signaling. Downregulated pathways: myeloid compartment. (**C**) Top hit was CCL21, which recruits CCR7+ naïve and central memory T cells. Additional hits are CXCL9, CXCL11, and CXCL13, which activate CXCR3 receptor expressed by T and NK cells (CXCL13 also recruits CD4+ T follicular cells that support B cell follicle formation). Top hit that was depleted is HDAC11, a negative regulator of type I interferon signaling (12 patients).

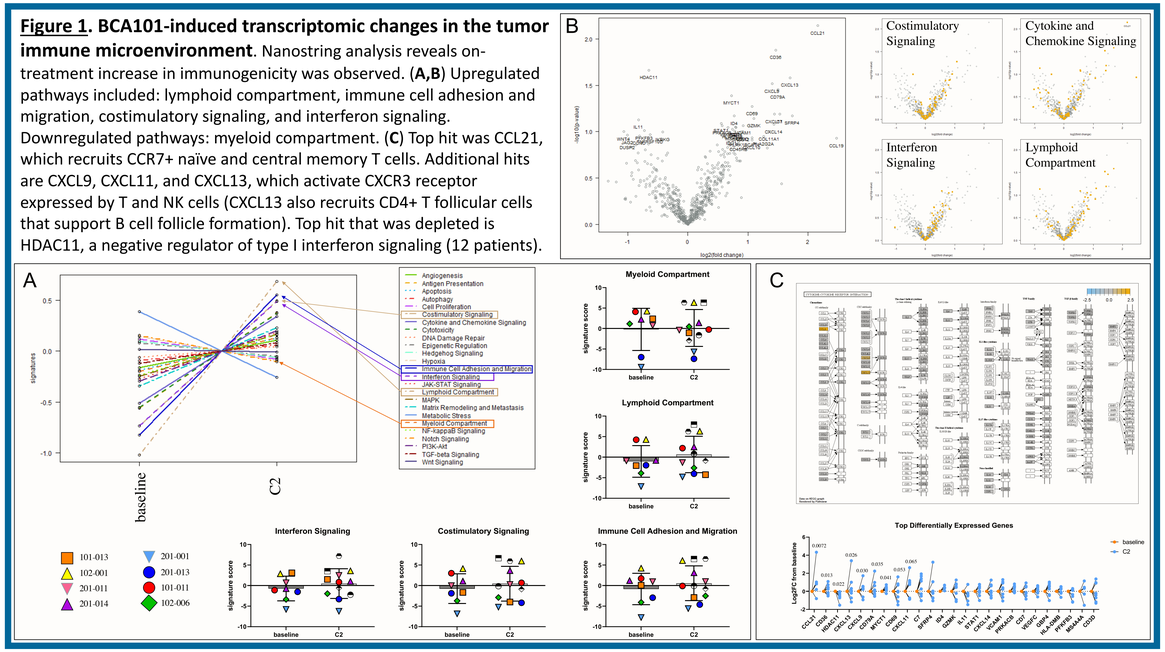


Figure 2. Multiplexed Ion Beam Imaging (MIBI™) of matched pre- and on-treatment samples reveals reduction in post-treatment immunosuppressive macrophages. Majority of CD45+ cells are myeloid cells. M2 macrophages were much more abundant than M1 in all samples. M2 (CD163-expressing) macrophages and monocytes (CD68+/-) decreased from baseline to C2 in 3/3 patients

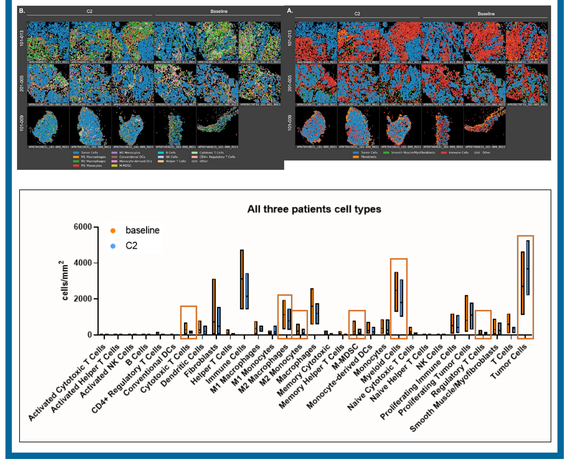


Figure 3. HLA-DR- circulating monocyte abundance is decreased in BCA101-treated patients. Pre- and on-treatment patient PBMCs were immunologically profiled by multiparametric flow cytometry for lineage and phenotypic markers. HLA-DR-negative CD14+ monocytic MDSC were significantly less abundant in the on-treatment samples from patients who maintained stable disease or experienced a partial response (46 patients).

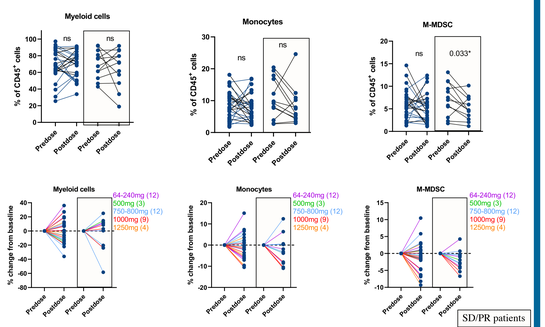
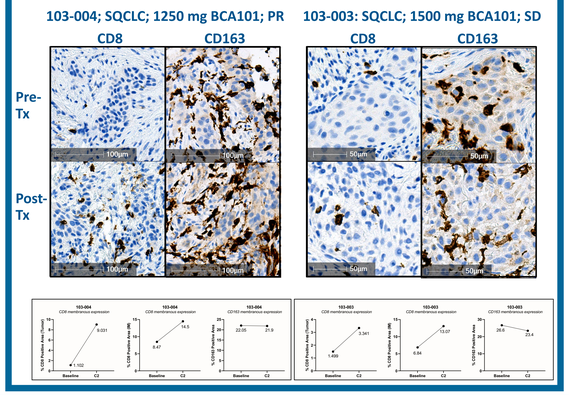


Figure 4. Favorable immune modulation following BCA101 single agent. Two patients with EGFR-amplified SqNSCLC were treated with BCA101 and achieved a partial response and prolonged stable disease, respectively. IHC revealed increased CD8+ T cells and a reduction in CD163+ TAMs post-treatment.



Conclusions: Decreased abundance of circulating HLA-DR- monocytes following treatment indicated polarization towards a more positive, Th1-like systemic immune state. We observed enhanced immunogenicity of tumors as assessed using a targeted transcriptomic analysis (Nanostring). The results of the pathway analysis were supported by multiplexed imaging analyses on post-treatment biopsies from a subsequent cohort showing enhanced CD8+ T cell infiltration and stable, or reduced expression of TAM marker CD163. These results indicate that BCA101 induces a more permissive tumor immune microenvironment.

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