BCA101, a Novel Tumor-Targeted Bifunctional Fusion Antibody Simultaneously Inhibiting EGFR and TGF-β Signaling with Potential for Durable Tumor Growth Inhibition

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Background

Given the pleiotropic functions of transforming growth factor-beta (TGF-β), current approaches to targeting systemic TGF-β will likely lead to suboptimal clinical activity and/or undesirable effects such as acute bleeding and cardiotoxicity. Epidermal growth factor receptor (EGFR) is one of the most extensively validated tumor-associated antigens. Bicara Therapeutics has developed a novel bifunctional fusion protein, composed of a monoclonal antibody against EGFR and an extracellular domain of human TGF-β receptor II (TGF-βRII). We demonstrate BCA101 has the potential to improve anti-tumor response by leveraging the cooperativity between EGFR and TGF-β signaling pathways by predominantly neutralizing TGF-β in EGFR-expressing tumors.

Figure 1: Mechanism of action of BCA101 beyond anti EGFR antibody

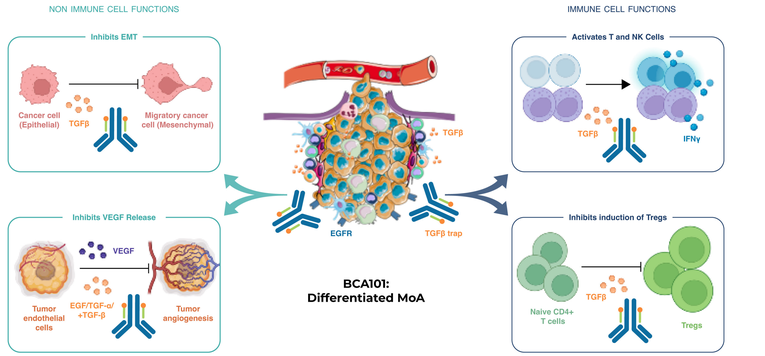
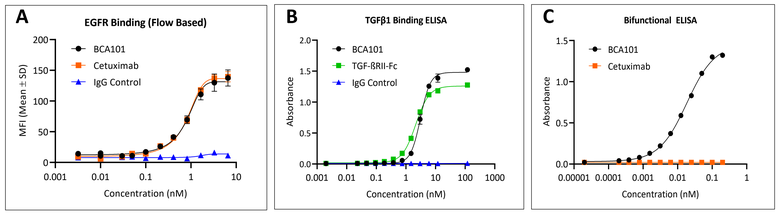
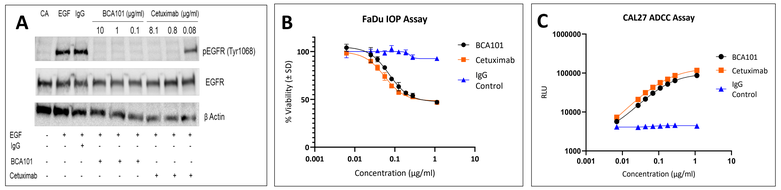


Figure 2: BCA101, a bifunctional antibody designed to target both EGFR and TGF-β simultaneously



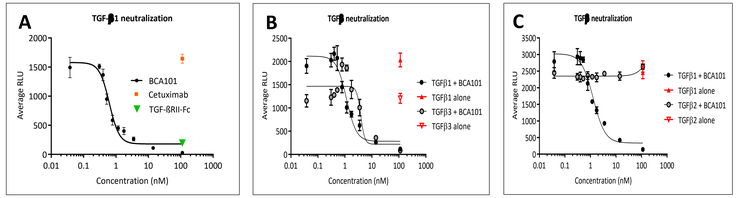
BCA101 binding to EGFRhigh FaDu cells by flow cytometry(A), TGF-β1 by ELISA (B) and both EGFR and TGF-β1 by bifunctional ELISA (C)

Figure 3: Functions of F(ab)$_2$ and Fc arms of BCA101



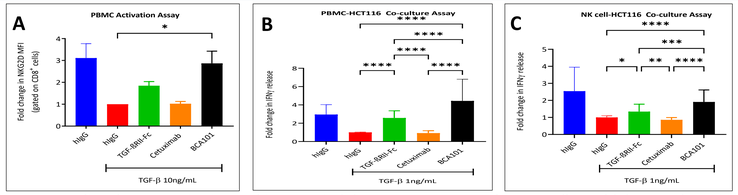
BCA101 mediated inhibition of phospho-EGFR in EGF stimulated FaDu cells evaluated by western blot (A), inhibition of proliferation (IOP) of FaDu cells (B), antibody dependent cell mediated cytotoxicity (ADCC) of CAL27 cells(C)

Figure 4: BCA101 neutralizes TGF-β1 and TGF-β3 but not TGF-β2



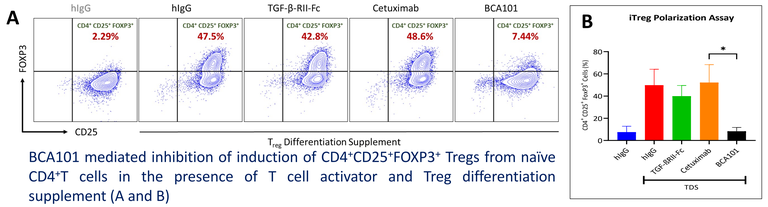
Neutralization of TGF-β by BCA101 using HEK-SMAD reporter cell line (A-C)

Figure 5: BCA101 rescues inhibitory effect of TGF-β and enhances cytolytic activity of PBMCs or NK cells against tumor cells



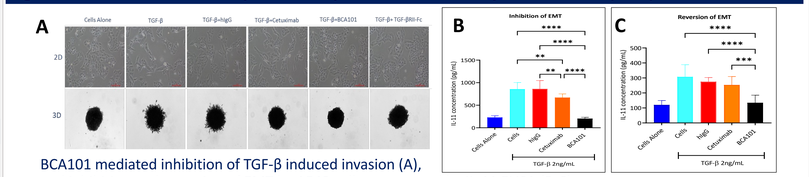
BCA101 mediated PBMC activation and increase in (A) NKG2D MFI on gated CD8$^+$T cells, and (B) IFNγ release in PBMC or NK cell co-culture with HCT116 cells(B-C)

Figure 6: BCA101 inhibits TGF-β1-mediated differentiation of naïve CD4$^+$T cells to induced T regulatory cells



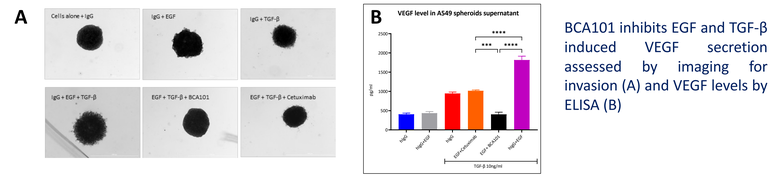
BCA101 mediated inhibition of induction of CD4$^+$CD25$^+$FOXP3$^+$ Tregs from naïve CD4$^+$T cells in the presence of T cell activator and Treg differentiation supplement (A and B)

Figure 7: BCA101 inhibits TGF-β induced epithelial to mesenchymal transition(EMT)



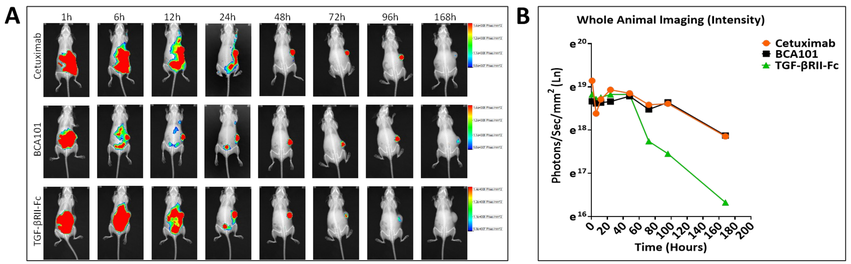
BCA101 mediated inhibition of TGF-β induced invasion (A), and inhibition and reversion of EMT by A549 cell as measured by IL-11 ELISA (B-C)

Figure 8: BCA101 blocks EGF and TGF-β synergistic effects in A549-PBMC co-culture model



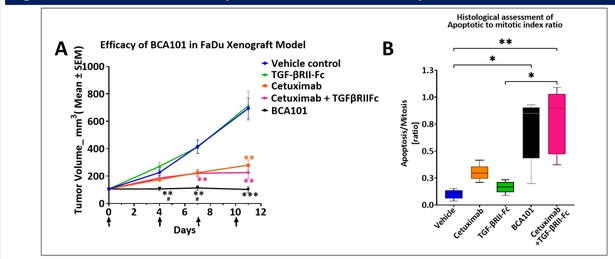
BCA101 inhibits EGF and TGF-β induced VEGF secretion assessed by imaging for invasion (A) and VEGF levels by ELISA (B)

Figure 9: BCA101 preferentially localizes to the tumor.



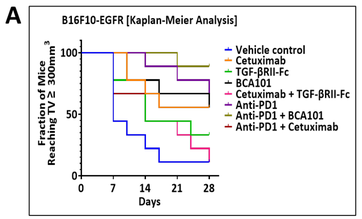
- In BCA101 and cetuximab dosed groups, the signal intensity in tumor ROI sustained till 96 hours and subsequently tapered off at 168 hours (Figure 9A and B).
- In TGF-βRII-Fc dosed group, the signal intensity was maintained till 48 hours and subsequently tapered off, and was not observable at 168 hours (A, B)

Figure 10: BCA101 shows superior anti-tumor efficacy over cetuximab in FaDu xenograft mice model.



The superior anti-tumor efficacy of BCA101 over cetuximab (A), could be associated with higher apoptotic bodies to mitotic index ratio (B)

Figure 11: BCA101 in combination with immune checkpoint therapeutics is highly efficacious in B16F10-EGFR xenograft mice model.



B

Group	# of mice with Tumor	p value	Significant
Vehicle	8	-	-
Cetuximab	5	0.2941	ns
TGF-βRII-Fc	6	0.5765	ns
BCA101	4	0.1312	ns
Cetuximab + TGF-βRII-Fc	8	>0.9999	ns
Anti-PD1	3	0.0498	*
Anti-PD1 + BCA101	1	0.0034	**
Anti-PD1 + cetuximab	3	0.0498	*

The combination of BCA101 with anti-PD1 showed the best response with only 1/9 mice achieving an event of TV ≥ 300 mm3 (A, B)

Conclusions

These results support clinical development of BCA101 as a targeted immunotherapy with potential to induce improved anti-tumor response with a wider therapeutic window, either as a monotherapy or in combination with immune checkpoint blockade therapy.

BCA101 is currently being evaluated in dose escalation studies as a monotherapy and in combination with pembrolizumab (anti-PD-1) - BCA101X1101 (NCT04429542).

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