Background Given the pleiotropic functions of transforming growth factor-beta (TGFβ), current approaches to targeting systemic TGFβ will likely lead to suboptimal clinical activity and/or undesirable effects. 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 TGFβ receptor II (TGFβRII). We demonstrate BCA101 has the potential to improve anti-tumor response by leveraging the cooperativity between EGFR and TGFβ signaling pathways while restricting TGFβ neutralization to EGFR-expressing tissues.

Methods Functional neutralization of TGFβ by BCA101 was demonstrated by several in vitro assays which assessed TGFβ-dependent epithelial to mesenchymal transition (EMT), cell invasion, inducible Treg differentiation, as well as allogeneic immune responses in tumor cell/immune cell coculture assays. In vivo, the anti-tumor efficacy of BCA101 was determined in tumor xenograft mouse models, using either human tumor cell lines or patient-derived tumor cells (PDX), as well as in a humanized mouse model.

Results In vitro, we showed BCA101 is capable of simultaneously binding EGFR and TGFβ with a significantly higher affinity for EGFR. The incorporation of the TGFβRII "trap" did not sterically interfere with the ability of BCA101 to bind EGFR, inhibit cell proliferation or mediate antibody-dependent cellular cytotoxicity (ADCC). Relative to cetuximab, BCA101 showed improved ability to reverse EMT and preserve ADCC activity. In tumor cell/immune cell co-culture assays, BCA101 increased production of proinflammatory cytokines associated with T and NK cell activation and suppressed VEGF release. Further, BCA101 inhibited differentiation of inducible Treg and displayed an immuno-potentiating profile in the BioMAP® TME model. In vivo, biodistribution studies showed that BCA101 localized to tumor tissues in xenograft mouse models, with comparable kinetics as cetuximab. TGFβ in tissues was neutralized to about 90% at 10 mg/kg of BCA101 while equivalent doses of TGFβRII receptor inhibited TGFβ in tumors by around 50%, confirming improved tumor localization with BCA101. In PDX models derived from head and neck cancer squamous cell carcinoma patients, BCA101 exerted sustained antitumor effect and delayed tumor growth compared to cetuximab. Finally, BCA101 improved the anti-tumor activity of PD1 blockade therapy in humanized HuNOG-EXL mice bearing PC-3 xenografts (figure 1).

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

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REFERENCES


Ethics Approval Mice were maintained as per the regulations of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) guidelines. All animal experiments were approved by institutional ethical committee and performed under approved protocols. For PDX model, head and neck cancer patient samples were obtained from Mazumdar Shaw Medical Foundation, Bengaluru, India after appropriate approvals were obtained from institutional ethical committee: NHH/MEC-RC2016-404

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