CRB-601, a selective integrin αvβ8-blocking antibody, prevents TGFβ activation, promotes immune cell remodeling, and exhibits potent antitumor activity

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Background

Increased TGFβ signaling is a key driver of tumor growth and immune cell exclusion. Thus, blocking TGFβ signaling has emerged as a challenging but essential node to regulate to prevent uncontrolled tumor proliferation.

TGFβ is thought to promote tumor progression via various mechanisms, including epithelial-mesenchymal transition associated with metastasis, neoangiogenesis that facilitates tumor vascularization, stromal cell and cancer-associated fibroblast proliferation, and immunosuppressive signaling. Collectively, TGFβ signaling alters the tumor microenvironment, contributes to immune exclusion, and renders tumors insensitive to many systemic treatments including checkpoint therapies.

An essential aspect of TGFβ activation is the structural changes that are induced by the binding the integrin αvβ8 to a homodimer of latent-TGFβ that is cell bound as a large latent complex (LLC). This binding exposes the active domain of the mature TGFβ protein enabling the binding and activation of the TGFβ-R2 and triggering TGFβ signaling.

The current investigation explored the impact of CRB-601 on tumor growth and the modulation of the immune milieu in murine syngeneic tumor models. We also explored the profile of biomarkers associated with an anti-tumor response across immune cell types, chemokines and cytokines.

Methods

The tumor growth inhibition of CRB-601 +/- anti-PD-1 was assessed in 3 tumor models, MC38, EMT6, and 4T1. Post treatment both tumors and peripheral blood were collected to conduct pharmacodynamic analyses.

Flow Cytometry was used as a primary method to analyze both the periphery and excised tumors for modulation of the immune cell populations. Additionally, tumor specimens underwent Bulk Sequencing and Luminescence cytokine assessment, which provided a multifaceted understanding of the tumor’s microenvironment and cytokine profile.

A specific immunological assessment, known as the IFNγ ELISPOT, was also performed on the splenics extracted from mice that were re-challenged with the MC38 tumor model to determine the immune system’s responsiveness and effectiveness in combating the re-introduced tumor cells.

Results

CRB-601 Enhances Anti-PD-1 Therapy in Checkpoint Inhibition Sensitive and Resistant Murine Tumor Models

Figure 2. αvβ8-blocking antibody CRB-601 enhances anti-PD-1 therapy in both immune checkpoint blockade therapy sensitive and resistant murine tumor models. A) MC38 (inflamed Tumor) B) EMT6 (Excluded Tumor) C) 4T1 (Desert Tumor)

The Increase in Activated CD8+ T Cells in Peripheral Blood Post CRB-601 Treatment Indicates That This Assessment is a Potential PD-Biomarker

Figure 3. In CRB-601 treated mice, an increase in activated effector CD8 T cells and central memory CD8 T cells in peripheral blood are observed, potentially serving as markers of response to CRB-601.

CRB-601 Treatment Elevates Cytotoxic T and Natural Killer Cells While Reducing Immunosuppressive Subsets in Murine Tumor samples

Figure 4. After a 10-day treatment with CRB-601, immune profiling reveals changes in T-cell and innate immune activities. In combination with anti-PD1, CRB-601 enhances cytotoxic effecter T-cells and NK cells while reducing PMNs.

CRB-601 Enriches the Effector Immune Cell Population in a Murine Tumor

Figure 5. Immune deconvolution of RNA bulk seq tumor samples after treatment with CRB-601 +/- anti-PD-1. Alterations in CD4+ T cells and monocytes/macrophages immune subsets within MC38 tumors.

Immunomodulatory Cytokines Within the Local Tumor Milieu are upregulated with CRB-601 +/- anti PD-1 treatment

Figure 6. CRB-601 +/- anti PD-1 treatment resulted in increased levels of IFNγ, RANTES, and MIPα signaling a heightened anti-tumor immune response

Figure 7. Evaluation of long-term antitumor immunity in cured mice after CRB-601 and anti-PD-1 combination treatment.

Principal component analysis of tumor samples (n=30) based on cytokine levels (n=36). The PCA biplot shows separation based on both the 1st and 2nd principal component between samples treated with either anti-mPD1, CRB-611 or combination therapy (CRB-611 and anti-mPD1) and the control group with the cytokines IL-31, IL-27, MIPα, CCL5/RANTES and IFNγ explaining majority of the variability in the data.

CRB-601 +/- anti-PD-1 treatment Induced A Long-Lasting Tumor-Specific Cytotoxic T Cells Response

Conclusion

CRB-601 advances immunotherapeutic strategies by antagonizing integrin αvβ8, enhancing the efficacy of immune checkpoint inhibitors in vivo.

The synergistic administration of CRB-601 with anti-PD-1 agents significantly enhances tumor-specific cytotoxic T-cell responses, suggesting an enriched T-cell precursor population. Concurrently, a noticeable reduction in PMN activity is observed, indicating a transition towards a less immunosuppressive tumor microenvironment. This favorable shift is further strengthened by the elevated IFNγ activity observed, which signals enhanced anti-tumor activity mediated by immune cells, showcasing a promising therapeutic synergy for improved cancer treatment outcomes.

This notable combination reveals the potential of such synergistic strategies in strengthening anti-tumor immunological responses, thereby emphasizing the promise of this combinational approach in advancing the domain of immunotherapy.

References


Disclosures and Acknowledgements

This study was sponsored by Corbus Pharmaceuticals, Inc. Authors MS, DW, VS, RB and AK are employees and/or shareholders of Corbus Pharmaceuticals.

SR, JB and SN are UCSF employees.

CRB-601 is an investigational, pre-clinical stage candidate that has not entered clinical testing and is not approved by the FDA for any indication.