Background In metastatic disease, Transforming growth factor-beta (TGFβ) signaling in the tumor microenvironment (TME) is associated with immune cell exclusion, checkpoint inhibitor resistance, and poor clinical outcomes. TGFβ, produced in latent form (L-TGFβ), requires activation upon integrin binding. Integrin αvβ8 demonstrates exquisite specificity for L-TGFβ activation. Corbus is developing a high-affinity monoclonal antibody, CRB-601, targeting integrin αvβ8, which inhibits cell-bound L-TGFβ activation.

Methods Mice bearing orthotopically implanted murine breast cancer EMT6 or subcutaneously implanted murine colon carcinoma MC38 were treated with CRB-601, an anti-PD1 antibody, or the combination. CRB-601’s effects on tumor growth, immune cell populations, and biomarkers of response (e.g., TGFβ levels, cell αvβ8 surface occupancy, and downregulation of SMAD2/3 phosphorylation) were evaluated. Also assessed were T-cell pharmacodynamics and memory response in the MC38 model.

Results CRB-601, as a monotherapy and in combination with anti-PD1, effectively inhibited tumor growth in both EMT6 and MC38 models. This treatment combination increased the percentage of T cells, Dendritic cells, and M1-like macrophages, suggesting a comprehensive reshaping of the TME. Biomarker analyses indicated a successful engagement with the target, integrin αvβ8, coupled with an efficient inhibition of TGFβ activation. The MC38 model demonstrated elevated levels of cytokines IL-2 and IL12p70, critical for T cell proliferation, differentiation, and activation. Furthermore, the combination therapy of CRB-601 and anti-PD1 reduced the levels of dysfunctional T cells while enriching effector T cells in the MC38 model. Mice treated with this combination therapy achieved complete remission, and the adoptive transfer of splenocytes led to enhanced anti-tumor activity.

Conclusions CRB-601 is a potent and selective integrin αvβ8-blocking monoclonal antibody that can overcome tumor immune cell exclusion and enhance the activity of immune checkpoint inhibitors in vivo. The encouraging results from this study, such as tumor growth inhibition and significant immune cell infiltration, hint at the potential of CRB-601 as a promising cancer immunotherapy. Investigational New Drug (IND) enabling studies are currently underway.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0833