CRB-601, A SELECTIVE INTEGRIN αvβ8 BLOCKING ANTIBODY, EXHIBITS POTENT ANTI-TUMOR ACTIVITY IN ANTI-PD-1 RESISTANT MODELS

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Background Transforming growth factors-beta (TGFβ) is a promising immunotherapeutic target in cancer given its association with increased signaling in the tumor microenvironment (TME) immune exclusion, resistance to checkpoint inhibitors (CPI), and poor clinical outcomes. TGFβ is expressed as a latent form (L-TGFβ) and presented on cell surfaces by L-TGFβ binding proteins (e.g. GARP and LTPB1) as part of the large latent complex (LLC) whereupon it is activated by binding to integrins. Integrin αvβ8 binds to and activates L-TGFβ, specifically the TGFb1 and TGFb3 isoforms. Corbus Pharmaceuticals is developing a humanized monoclonal antibody, CRB-601, that binds with high specificity and affinity to integrin αvβ8 and blocks its critical interaction with L-TGFβ.

Methods Mice bearing subcutaneously implanted murine colon carcinoma MC38 or orthotopically implanted murine breast cancer EMT6 and 4T1 were treated with αvβ8-blocking antibody CRB-601, anti-mouse PD-1 or the combination. These models demonstrate differential sensitivity to CPI treatment and are thought to reflect an immune inflamed (MC38), excluded (EMT6) or desert (4T1) tumor immune phenotypes. To determine the impact of disease establishment on sensitivity of these models to CRB-601 treatment both early (tumor volume = 50-80 mm³) and late (tumor volume > 200 mm³) intervention studies were conducted. Tumor growth, immune cell populations, and biomarkers of response (e.g. TGFb levels) were evaluated.

Results CRB-601 as a single agent, significantly inhibited growth of both MC38 and EMT6 models in both early and late intervention studies. In combination with anti-PD-1, CRB-601 not only enhanced anti-PD-1 therapy efficacy in early- and late-stage immune inflamed MC38, but also overcame resistance to PD-1 therapy in late-stage immune excluded EMT6 model. Notably, in the 4T1 model, an anti-PD-1 resistant desert tumor, combination therapy with CRB-601 and anti-PD-1 resulted in significant tumor growth inhibition even though there was negligible effect of each single agent. Analysis of tumor infiltrating lymphocytes in treated EMT6 tumors, showed TME remodeling, marked by increased infiltration of T cells, NK cells and M1-like macrophages in animals receiving CRB-601 or the combination. Biomarkers of response were consistent with Integrin αvβ8 target engagement.

Conclusions CRB-601 is a potent and selective integrin αvβ8 blocking monoclonal antibody that can overcome tumor immune exclusion and enhance the activity of immune checkpoint inhibitors in vivo. Investigational New Drug (IND) enabling studies are currently underway.