1388 CRB-601, AN INTEGRIN αVβ8 BLOCKING ANTIBODY ENTERING PHASE I: PRE-CLINICAL AND TRANSLATIONAL BIOMARKERS FOR INDICATION SELECTION

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Background TGFβ is a cytokine associated with immunosuppression in many metastatic solid tumors. Despite the known role that this pleotropic cytokine can play in tumor promotion, efforts to target this pathway have been hampered by on-target toxicities, pathway redundancies and challenges in achieving tumor specific drug concentrations.

TGFβ is produced as a membrane bound latent protein (L-TGFβ) in which TGFβ is held in an inactive complex with its pro-peptide, latency associated protein (LAP) and one of several latent -TGFβ binding proteins. Integrin $a_v\beta_8$ is a key activator of L-TGFβ acting in the context of solid tumors at the synapse between tumor and immune cells. CRB-601 is a high affinity IgG4 monoclonal antibody with selectivity for integrin $a_v\beta_8$ and blocks its activation-inducing interaction with L-TGFβ. A Phase 1 study to investigate the safety, pharmacokinetics, and efficacy of CRB-601 in patients with advanced solid tumors is in planning.

Methods Anti-tumor activity, immunological changes and biomarkers of response were evaluated in pre-clinical mice models. These models representing differential sensitivity to anti-PD-1 therapy and tumor immune landscapes: immune inflamed (MC38), excluded (EMT6) or desert (4T1). CRB-601 efficacy in these models was correlated with modulation of immune cell populations in tumor and blood using flow cytometry, genomic, cytokine/chemokine analysis and immunohistochemistry. Assessment of protein expression of $a_v\beta_8$ and TGFβ pathway related genes was used to evaluate solid tumors.

Results Both MC38 and EMT6 models showed significant tumor grown inhibition with CRB-601 as a single agent and in combination with anti PD-1. Treatment with the combination in the 4T1 desert model resulted in statistically significant tumor inhibition whereas the individual treatments had no effect. Increase in infiltration of T cells, NK cells and M1-like macrophages upon treatment were observed in the tumor microenvironment. Furthermore, in peripheral blood, a 2-fold increase was observed in the population of effector CD8+ T cells. Similarly, cytokine/chemokine, genomic analysis, and pSMAD2/3 protein levels in tumors showed modulation upon treatment with CRB-601 suggestive of the ability of CRB-601 to control immune system activation mediated by local TGFβ concentrations.

Conclusions Pre-clinical studies demonstrate that CRB-601 is a potent and selective integrin $a_v\beta_8$ blocking mAb that demonstrates immunomodulatory effects reflected in changes in the tumor lymphocyte population, cytokine profile and gene expression. Understanding gene and protein expression levels for various solid tumors may enable rational indication selection.

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