The TAM family of receptor tyrosine kinases (RTKs), TYRO3, AXL, and MER, has emerged as attractive targets for cancer immunotherapy. In immune cells, TAM RTKs play a key homeostatic role in maintaining regulatory immune checkpoints that prevent cancer cells from immune surveillance. Thus, targeted inhibition of TAM has the potential to restore and enhance host defense against cancer.

RXDX-106 is a potent small molecule inhibitor of TYRO3, AXL, and MER with biological IC50 values of 2.46 nM, 3.54 nM and 0.60 nM, respectively. In a binding kinetics study, RXDX-106 displayed slow dissociation from the targets, leading to more durable target inhibition.

RXDX-106 demonstrated single agent anti-tumor activity in multiple syngeneic tumor models. When subcutaneous models of MC38, EMT-6 and Renca were established in both immuno-competent mice, RXDX-106 treatment resulted in more potent inhibitory responses in all three tumor systems grown in immuno-competent hosts, confirming immune-mediated anti-tumor efficacy of RXDX-106. Specifically, the inhibition of tumor growth in the MC38 syngeneic model was associated with increases in tumor infiltrating lymphocytes (TIL), M1-polarized macrophages, and COX-2 and IFN-γ expression on NK cells. In addition, as an in vivo study using metastatic tumor cells indicated enhanced tumor immune cell function post RXDX-106 treatment. When administered in combination regimens, RXDX-106 potentiated the anti-tumor activity of anti-tumor microenvironment. The unique mechanism of activating both innate and adaptive immunity by RXDX-106 supports clinical development of RXDX-106 as an immuno-oncology agent.

**RESULTS**

**Increased Expression of TAM RTKs in the MC38 Tumor Microenvironment as a Rationale for Pan-TAM RTK Inhibition**

In vivo Anti-Tumor Effect of RXDX-106 on Syngeneic MC38 and CT26 Models in Combination with Anti-PD-1 Antibodies

**CONCLUSIONS**

- RXDX-106 is a potent inhibitor of TYRO3, AXL, and MER with a slow off rate leading to durable target inhibition.
- RXDX-106 showed greater tumor growth inhibition in immuno-competent mice than in immuno-deficient mice, indicating involvement of host immunity in mediating RXDX-106 efficacy.
- RXDX-106 treatment led to increased total TIL and M1 polarization in the tumor, as well as increased NK function.
- AXL and MER expression increased on both tumor and immune cells during tumor progression and inhibition of TAM RTK activity in vivo. RXDX-106 inhibited AXL, MER, or GAS6 expression on tumor cells, leading to repolarization of the immune response towards an anti-tumor microenvironment.
- The unique mechanism of activating both innate and adaptive immunity by RXDX-106 supports clinical development of RXDX-106 as an immuno-oncology agent.