**SUMMARY**

The TAM family of receptor tyrosine kinases (RTKs), TYRO3, AXL, and MER, has been implicated in the pathogenesis and progression of many cancerc types. Abnormally elevated TAM signaling is associated with cancer progression, metastasis, and drug resistance. Particularly in immune cells, RTKs play a key homeostatic role as negative regulators of immune responses, contributing to the evasion of cancer cells from immune surveillance. Thus, targeted inhibition of TAM receptors has emerged as a potential novel strategy for cancer treatment by restoring and enhancing host immunity against cancer.

RXDX-106 is a selective and potent TAM RTK inhibitor in preclinical development. Previously, we have reported functional modulation of TAM RTKs on immune cells in the tumor microenvironment. We also demonstrated an anti-tumor effect of RXDX-106 in the CT26 syngeneic mouse model in combination with anti-CTLA-4 antibody. Here, in the MC38 syngeneic model, RXDX-106 treatment resulted in significant tumor growth inhibition and survival benefit, whereas such benefit was reduced when the tumors grew in immunocompromised athymic nude mice. The inhibition of tumor growth in the syngeneic model was associated with an increase in activated intratumoral CD4 T cells, increased expression of CD69 and PD-1 on CD8 T cells, all indicative of activation of cytotoxic T cells. In addition, M1 polarization of tumor-associated macrophages, an increase in CD169+ antigen presenting macrophages, and upregulation of CD69 and PD-L1 were observed. In another syngeneic model, CT26, RXDX-106 inhibited tumor growth as a single agent, and the combination with anti-PD-1 demonstrated further tumor growth inhibition. RXDX-106 also increased IFN-γ levels in the blood in combination with either anti-PD-1 or anti-CTLA-4 antibodies. Real-time PCR revealed that RXDX-106 upregulated antitumor genes perforin (Prf1) and granzyme B (GrzB) predominantly expressed by cytotoxic T lymphocytes. Finally, luminescence analysis of tumor cell lysates revealed an upregulation of anti-tumor cytokines by RXDX-106 in combination with anti-PD-1 antibody.

**RESULTS**

**Mechanism of Action of RXDX-106 as an IO agent: a working model**

**CONCLUSIONS**

- **RXDX-106** is a highly potent, pseudo-irreversible inhibitor of TAM family RTKs.
- **RXDX-106** showed greater tumor growth inhibition in immunocompetent mice than in athymic nude mice, indicating potential involvement of T cells in mediating RXDX-106 efficacy.
- **RXDX-106** demonstrated tumor growth inhibition as a single agent and potentiated the anti-tumor effect of checkpoint inhibitors to achieve greater efficacy.
- In vivo, RXDX-106 modulated multiple immune cell populations, including macrophages and T cells, towards an anti-tumor microenvironment.