ABSTRACT

After decades of research, covalent inhibitors targeting KRASG12C are entering clinical trials. KRASG12C mutations are found in 34% of non-small cell lung cancer (NSCLC) adenocarcinomas as well as several other cancer types at lower frequencies. KRASG12C mutations are smoking-associated transversion mutations that are associated with a relatively high total mutation burden (TMB) and PD-L1 positivity. Although preclinical models are clinically active in KRAS mutant NSCLC, response rates remain modest and strategies to augment the clinical activity of checkpoint inhibitor (CI) therapy in an era of major clinical investigation, MRTX849 was identified as a potent, selective, and covalent inhibitor presently in clinical development. To evaluate the potential of MRTX849 to augment CPI therapy, the impact of MRTX849 on immune signaling molecules and response to anti-PD-1 therapy was evaluated. In a panel of human xenograft models, MRTX849 increased PD-L1 expression and decreased RNA and circulating protein expression of signaling molecules including VEGFA, CXCL1 and CXCL8, demonstrating MRTX849 modulates factors that are implicated in antigen presentation or an immunosuppressive tumor microenvironment through a tumor cell-mediated mechanism. In CT26G12C-engineered mouse models expressing KRASG12C, MRTX849 decreased intratumoral immunosuppressive myeloid-derived suppressor cells (MDSC) populations and promoted immune enhancing M1 polarized macrophages doublet, CD4+ and CD8+ T cell populations when administered as a single agent. These effects were also observed in tumors from MRTX849 plus anti-PD-1 treated mice. In efficacy studies, MRTX849 plus anti-PD-1 treatment resulted in durable, complete responses in six out of ten xenografts whereas all but one of the tumors eventually progressed in the anti-PD-1 single agent treatment group. To further determine the mechanism of response to the combination, the six mice with complete responses were re-challenged with CT26KRASG12C and tumors failed to demonstrate a combination-treated mice developed durable anti-tumor immunity. In summary, these data demonstrate MRTX849 in combination with anti-PD-1 therapy leads to durable complete regressions through an immune-mediated anti-tumor response.

MRTX849 is a Novel, Covalent KRASG12C Inhibitor

MRTX849 is a KRASG12C inhibitor that covalently binds mutant Cys12 in the KRASG12C-QP pocket, KRASG12C, blocks KRAS signaling, and inhibits tumor growth.

MRTX849 Modifies Tumor Cell-Intrinsic Factors that Regulate Antigen Presentation and An Immunosuppressive Tumor Microenvironment

MRTX849 Treatment Regulates the Tumor Immune Microenvironment and Leads to Durable Complete Responses in Combination with Anti-PD-1 Therapy in a Syngeneic Mouse Model

REFERENCES