The KRAS<sub>G12C</sub> Inhibitor MRTX849 Reconditions the Tumor Immune Microenvironment and Leads to Durable Complete Responses in Combination with Anti-PD-1 Therapy in a Syngeneic Mouse Model

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ABSTRACT

After decades of research, covalent inhibitors targeting KRAS<sub>G12C</sub> are entering clinical trials. KRAS<sub>G12C</sub> mutations are found in 14% of non-small cell lung cancer (NSCLC) adenocarcinomas as well as several other tumor types at lower frequencies. KRAS<sub>G12C</sub> mutations are smoking-associated transition mutations that are associated with a relatively high tumorigenesis burden (TNM) and PD-L1 positivity. Although pancreaticobiliary is clinically active in KRAS-mutant NSCLC, response rates remain modest and strategies to augment the clinical activity of checkpoint inhibition (CI) are of an urgent clinical need. MRTX849 was identified as a potent, selective, and covalent KRAS<sub>G12C</sub> inhibitor presently in clinical development. To evaluate the potential of MRTX849 to augment CI 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 MHC Class I protein expression and decreased RNA and circulating protein expression of signaling molecules including VEGFA, CXCL1 and CXCL8, demonstrating MRTX849 modulates factors that are important in antigen presentation or an immunosuppressive tumor microenvironment through a tumor-cell mediated mechanism. In a CT26 syngeneic mouse model, reconditioning of a KRAS<sub>G12C</sub> KRAS inhibition may therefore reverse the immunosuppressive tumor microenvironment on oncogenic KRAS have been hypothesized including silencing of antigen presentation including in KRAS-mutant NSCLC (Borghaei, 2015; Garon, 2015). In this study, intraperitoneal (i.p.) inoculation of CT26.WT clone E3 with 10<sup>6</sup> G12C cells into the left flank in the one MRTX849-treated mouse and the six combination-treated mice showed the Tumor Cell Intrinsic Factors that Regulate Antigen Presentation and an Immunosuppressive Tumor Microenvironment

MRTX849 modifies tumor cell intrinsic factors that recondition the tumor immune microenvironment and lead to durable complete responses (CRs) of the tumors from the first implant. A cohort of naïve mice were naïve control (N=14), MRTX849 alone (N=6) and MRTX849 plus anti-PD-1 (N=6). MRTX849 / PD-1 combination-treated mice with durable, complete responses did not form tumors when re-challenged with CT26 KRAS<sub>G12C</sub> cells, whereas naïve mice developed tumors normally, demonstrating the combination resulted in an anti-tumor adaptive immune response.

MRTX849 is a Novel, Covalent KRAS<sub>G12C</sub> Inhibitor

MRTX849 is a KRAS<sub>G12C</sub>-selective, irreversible, covalent inhibitor that covalently binds cysteine 12 in the C-terminal domain of KRAS<sub>G12C</sub>, blocks KRAS signaling and tumor growth. MRTX849 is a novel, covalent KRAS<sub>G12C</sub> Inhibitor that Regulate Antigen Presentation and an Immunosuppressive Tumor Microenvironment

MRTX849 Treatment Reconditions the Tumor Immune Microenvironment by Modulating Key Immune Cell Types

MRTX849 modifies tumor cell intrinsic factors that recondition the tumor immune microenvironment and lead to durable complete responses (CRs) of the tumors from the first implant. A cohort of naïve mice were naïve control (N=14), MRTX849 alone (N=6) and MRTX849 plus anti-PD-1 (N=6). MRTX849 / PD-1 combination-treated mice with durable, complete responses did not form tumors when re-challenged with CT26 KRAS<sub>G12C</sub> cells, whereas naïve mice developed tumors normally, demonstrating the combination resulted in an anti-tumor adaptive immune response.

T Cell Frequency and Diversity are Increased in Response to MRTX849 and PD-1 Combination Treated CT26.WT Clone E3 Tumor Bearing Mice

CONCLUSIONS

- MRTX849 is a novel, mutant-selective, covalent KRAS<sub>G12C</sub> Inhibitor in clinical development with strong rationale for combining checkpoint inhibitor therapy.
- MRTX849 treatment alters tumor RNA and protein expression of factors implicated in presentation of tumor antigens and/or mediating an immunosuppressive tumor microenvironment in multiple KRAS<sub>G12C</sub>-mutant human xenografts.
- A CT26 model engineered to express RAAS<sub>G12C</sub> was dependent on KRAS for tumor cell growth and survival and was sensitive to MRTX849 treatment in vitro and in vivo.
- MRTX849 alone and in combination with an anti-PD-1 antibody decreased intra-tumoral immuno-suppressive MD-1 polarized macrophages, M1- and M2-MF and increased immune-potentiated M1-polarized macrophages, dendritic cells, CD4<sup>+</sup> and CD8<sup>+</sup> T-cells populations whereas adenovirus therapy failed to form, demonstrating 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.

REFERENCES