**BACKGROUND**

- KRAS G12C is an oncogenic driver mutation that is causative for disease but efforts to directly target KRAS have been historically challenging.
- MRTX1257 is a potent selective pan-KRAS G12C inhibitor that bridges structure-based drug design with high-throughput screening to identify cell potency, favorable oral properties, and low nanomolar cell potency.

**RESULTS**

**MRTX1257 Demonstrates Robust Tumor Growth Inhibition with a Dose-Dependent PKPD Relationship between KRAS Modification, Inhibition of KRAS-Driven Signaling, and Anti-Tumor Activity**

- **Figure 1B** Customized "synergyfinder" 96-well; 3-7 day proliferation
- **Figure 1C** Background

**MRTX1257 Inhibits pERK and 4E6 in H358 Tumors: Defects are Diminished After Multiple Dosing Days in H358 Tumors**

**MRTX1257 Demonstrates Broad Anti-Tumor Efficacy in KRAS G12C Mutant Cell Lines and Patient Derived Xenografts with Evidence of Adaptation to Treatment Observed in a Subset of Models**

**REFERENCES & ACKNOWLEDGEMENTS**

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**CONCLUSIONS**

- MRTX1257 potently and selectively inhibits KRAS-dependent signal transduction and viability of KRAS G12C mutant cell lines grown under 2D and 3D conditions.
- MRTX1257 administered daily PO at well tolerated dose levels induced 30% or greater tumor growth inhibition in most models. % change from baseline is calculated as tumor growth inhibition on a scale of 0-100 (0 = no change, 100 = complete regression).
- Feedback signaling through HIF-1α, VEGF overexpression of KRAS from cell cycle entry, and escape mechanisms may be responsible for single agent KRAS G12C treatment and may act additively through chemotherapeutic or immune checkpoint inhibitors.
- MRTX1257 KRAS G12C + Radiation Enhances Antitumor Activity of MRTX KRAS G12C - Particularly in Tumors Exhibiting CDK2A1 Deletions.