**BACKGROUND**

- KRAS G12C is an established driver mutation but efforts to directly target KRAS have been historically challenging.
- MRTX1257 is a mutant-selective, covalent inhibitor of KRAS G12C identified through structure-based drug design with low nanomolar cell potency and favorable oral PK properties.
- The anti-tumor activity and mechanism-of-action of MRTX1257 was evaluated across a panel of KRAS G12C-mutant and non-G12C mutant pre-clinical models and demonstrated selective KRAS-dependent antitumor activity in vitro and in vivo.
- Molecular mechanisms of therapeutic sensitivity and resistance were evaluated and selected resistance hypotheses were probed through combinatorial treatment strategies.

**RESULTS**

- Mouse F = 31.1%
- KRAS G12C H358 pERK IC50
- FF adj. IC50 = 0.035ug/mL
- Mouse PPB = 99%

**REFERENCES & ACKNOWLEDGEMENTS**

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**CONCLUSIONS**

- MRTX1257 is a research tool molecule that potentially and selectively inhibits KRAS G12C-dependent signal transduction in vitro and in vivo.
- MRTX1257 demonstrated activity in the majority of cell lines (18 of 23 cell lines) and in patient-derived xenograft models with durable complete response observed in some models (e.g., MIA Paca-2).
- Comprehensive pharmacodynamic and pharmacogenomic profiling identified potential mechanisms responsible for the incomplete responses seen in a subset of models.
- Feedback signaling through HER family RTKs, upregulation of KRAS G12C protein, and mTOR mediated bypass signaling were identified as top mechanisms for decreased response to single agent KRAS G12C treatment.
- Combinations addressing these resistance mechanisms augmented the activity of KRAS G12C inhibition in multiple models.
- With MRTX1257 demonstrated comparable selective activity in KRAS G12C mutant disease models and is presently under evaluation in clinical trials.