The Anti-Tumor Activity of the KRAS\(^{G12C}\) Inhibitor MRTX849 is Augmented by Cetuximab in CRC Tumor Models

Jill Hallin, Lauren Hargis, Lars D. Engstrom, Andrew Calinisan, Ruth Aranda, David M. Briere, Niranjan Sudhakar, Vickie Bowcut, Peter Olson, James G. Christensen

Mirati Therapeutics, Inc. San Diego, CA

Abstract 
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Background

• MRTX849 is a potent, selective, and conserved KRAS\(^{G12C}\) inhibitor presently under evaluation in clinical trials.

• MRTX849 only inhibits inactive GDP-bound KRAS\(^{G12C}\), which is known to be dependent on nucleotide cycling to regulate the activation state of KRAS.

• Comprehensive work in tumor xenograft models shows activation of pathways upstream or downstream of KRAS through additional mutations or relief of feedback inhibition can limit the single agent activity of MRTX849 in less responsive tumors.

• Activation of RTKs through relief of feedback inhibition is one key mechanism implicated in limited responses to KRAS\(^{G12C}\) inhibitors and the EGFR inhibitor, cetuximab, and SHP2 inhibitor, RMC-4550, both impact RTK signaling. Moreover, EGFR functions as a dominant RTK in colorectal cancer.

• The combination of MRTX849 and cetuximab or RMC-4550 in CRC models demonstrated increased KRAS\(^{G12C}\) modification and RAS/MEK pathway inhibition.

• A promising in vitro and preclinical model for KRAS\(^{G12C}\) CRC cancers is the NCI-H120 cell line and its xenograft model. This cell line is KRAS\(^{G12C}\)-mutant and has activating mutations in both PIK3CA and NRAS. It is non-responsive to KRAS\(^{G12C}\) inhibitors, and the combination of both compounds. Quantitation of band density performed for Active Ras.

• These data suggest that co-targeting KRAS\(^{G12C}\) and upstream targets like EGFR or G12C can result in limited responses to KRAS\(^{G12C}\).

Conclusions

• MRTX849 is a potent, selective, and conserved KRAS\(^{G12C}\) inhibitor presently under evaluation in clinical trials in NSCLC, CRC, and other tumor types with confirmed KRAS\(^{G12C}\) mutations.

• Activation of RTKs upstream of KRAS may be a key mechanism that limits the single agent activity of KRAS\(^{G12C}\) inhibition, especially in CRC tumor types.

• MRTX849 treatment in combination with cetuximab or RMC-4550 can more fully inhibit mutant KRAS\(^{G12C}\) signaling, which leads to more robust pERK modulation in vitro, and deeper, more durable regressions in CDX and PDX models in vivo.

• Co-targeting KRAS\(^{G12C}\)\(\) and EGFR or SHP2 are likely critical strategies to overcome resistance to single agent KRAS\(^{G12C}\) inhibition in CRC.

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