Effects of Adagrasib on Cholesterol, Lipid, and Glucose Gene Expression Regulation In Tumor Xenograft Models And Patient Samples

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BACKGROUND

Clinically active KRAS^{G12C} inhibitors have represented a key research breakthrough and led to novel treatment options for lung, colorectal and other cancer patients harboring this mutation. While treatment with KRAS^{G12C} inhibitors are clinically active in the majority of patients, the depth and duration of response is variable and most patients ultimately progress. This variation in therapeutic response highlights the need for a better understanding of drug mechanism of action and the identification of rational combination strategies. Oncogenic KRAS mutations hyperactivate the MAPK pathway, create an immunosuppressive tumor microenvironment, and promote glycolysis even in the presence of oxygen commonly known as the Warburg effect. This altered metabolic state is marked by increased glucose uptake and lactate production, providing necessary substrates for rapid tumor growth.

Emerging data suggested that lung cancer has elevated cholesterol requirements and that HDL-dependent cholesterol-efflux is impaired in KRAS-mutant lung cancers in mice and NSCLC patients[1,2]. Indeed, a recent study reported plasma HDL-C was 25% lower in lung cancer patients compared with healthy or chronic obstructive pulmonary disease (COPD) patients, and upregulation of HDL-mediated cholesterol efflux or increased cholesterol removal delayed tumor progression[1].

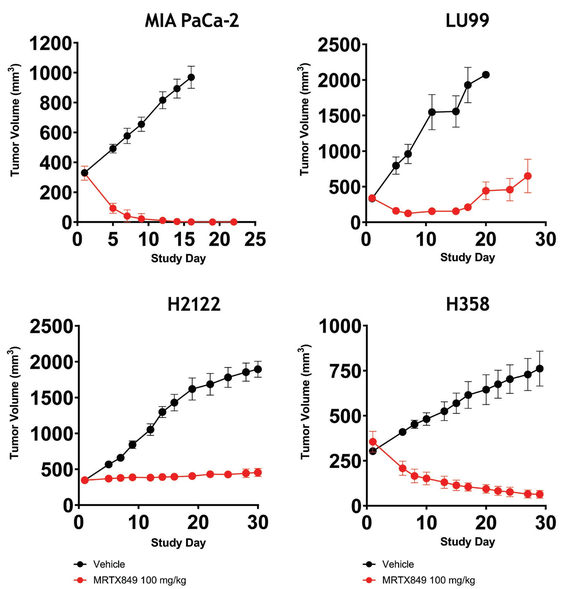
Our results show that pharmacological inhibition of mutant KRAS with the KRAS^{G12C} inhibitor adagrasib (MRTX849) revealed marked alterations of metabolic gene expression programs in tumor samples collected from mouse xenograft studies and repeat biopsies provided by patients enrolled on adagrasib clinical trials. Upregulation of genes involved in reverse cholesterol transport including *APOE, NR1H3* (*LXRa*) and *ABCA1* was observed across both preclinical tumor xenografts and patient samples following adagrasib treatment. Additionally, decreased expression of *SLC2A1* (*GLUT1*) and low-density lipoprotein receptor (*LDLR*) genes were also observed in both tumor models and patients suggesting that adagrasib treatment results in an extensive shift in the uptake and utilization of cholesterol, lipid, and glucose. Experiments are ongoing to investigate the impact of adagrasib treatment on circulating metabolic parameters in tumor xenograft-bearing mice in order to further elucidate the mechanism of action. Taken together, these data suggest adagrasib modulates cholesterol efflux, glucose and lipid pathways and alters tumor and systemic metabolic regulation. Additional research is needed to identify potential collateral vulnerabilities and rational combinatorial strategies.

Adagrasib (MRTX849) results in robust and durable tumor regression in KRAS^{G12C} xenograft models

Figure 1. Tumor growth inhibition with adagrasib treatment in KRAS^{G12C} pancreatic and NSCLC xenograft models

Vehicle or adagrasib at 100 mg/kg daily was administered orally to mice bearing MIA PaCa-2, LU99, H2122, or H358 cell line derived xenograft tumor models (n=5 mice/group) for 20-30 days.

Mean tumor volume +/- SEM is plotted.



Hallmark gene expression signatures in NSCLC xenograft models and patient samples following adagrasib treatment include KRAS dependent and metabolic pathway genes

Figure 2. Top most differentially expressed pathways in NSCLC xenograft models and NSCLC patient samples includes E2F, MYC targets, and cholesterol homeostasis

Mice bearing LU99 or H2122 xenograft tumors were treated with vehicle or adagrasib at 100 mg/kg for 6 or 7 days, respectively, and analyzed by RNAseq.

79 biopsy samples (70 NSCLC screening and 9 NSCLC C1D8 samples) from adagrasib treated patients were run on the HTG EdgeSeq Transcriptome panel (HTG Molecular).

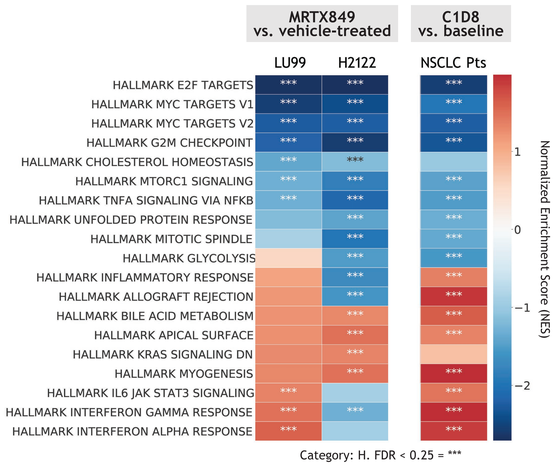
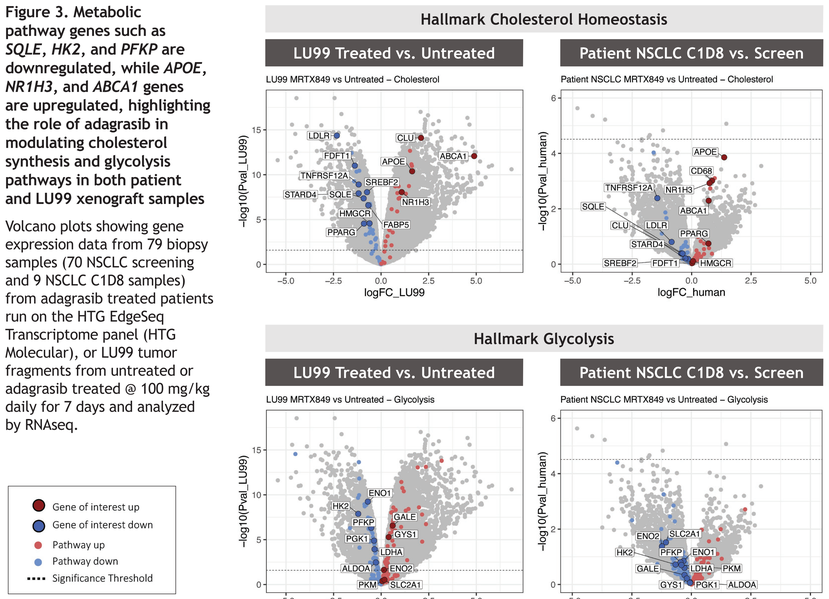


Figure 3. Metabolic pathway genes such as *SQLE*, *HK2*, and *PFKP* are downregulated, while *APOE*, *NR1H3*, and *ABCA1* genes are upregulated, highlighting the role of adagrasib in modulating cholesterol synthesis and glycolysis pathways in both patient and LU99 xenograft samples

Volcano plots showing gene expression data from 79 biopsy samples (70 NSCLC screening and 9 NSCLC C1D8 samples) from adagrasib treated patients run on the HTG EdgeSeq Transcriptome panel (HTG Molecular), or LU99 tumor fragments from untreated or adagrasib treated @ 100 mg/kg daily for 7 days and analyzed by RNAseq.



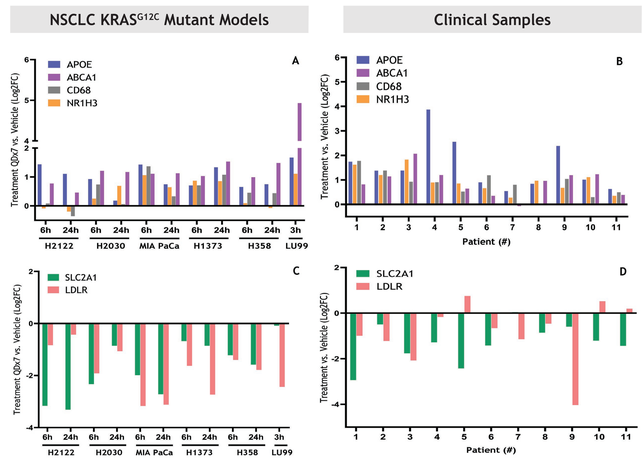
Adagrasib treatment alters expression of key lipoprotein and metabolic regulators in tumor xenografts and patient samples

Figure 4. *ApoE*, *NR1H3* (LXRα), *CD68*, and *Abca1* are upregulated following adagrasib treatment suggesting activation of reverse cholesterol transport. *SLC2A1* (Glut1) and *LDLR* gene levels are downregulated by treatment suggesting decreased lipid and glucose uptake

Mice bearing human NSCLC xenograft tumors were treated with vehicle or adagrasib at 100 mg/kg dosed daily by oral administration for 7 days.

Tissue was collected at 3 hours post last dose for LU99, and at 6 and 24 hours post last dose for all other models and analyzed by RNAseq.

11 matched patient tumor biopsy samples from baseline (screening) and adagrasib-treated C1D8 samples were run on the HTG EdgeSeq Transcriptome panel (HTG Molecular).



CONCLUSIONS

- Adagrasib inhibits KRAS-dependent signaling leading to tumor regression in multiple KRAS^{G12C} mutant cancer cell line xenograft models
- Metabolic pathway alterations detected in tumor samples collected from mouse xenograft studies treated with adagrasib and repeat biopsies provided by patients enrolled on adagrasib clinical trials
- Upregulation of genes involved in reverse cholesterol transport and decrease of genes critical to glucose and lipoprotein transport was observed across both preclinical tumor xenografts and patient samples following adagrasib treatment
- The functional impact of altered expression of key proteins and transporters after treatment with adagrasib on cholesterol, lipid and glucose levels in serum and tumor is the focus of current studies
- Additional investigation of a cholesterol lowering drug, such as an HMG-CoA reductase inhibitor, in combination with adagrasib, may provide additional benefit by impacting the MAPK and cholesterol pathways and is the focus of current studies

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