

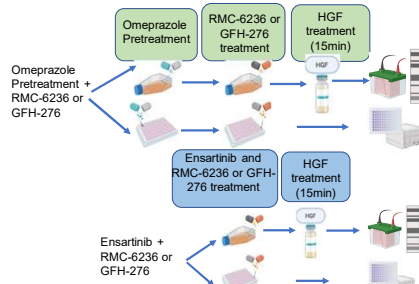
EP02.01: PanRAS(ON) inhibitors RMC-6236 and GFH276 in combination with omeprazole or ensartinib in KRAS-mutant lung cancer.

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INTRODUCTION

- KRAS G12C (OFF) inhibitors, such as sotorasib, are approved targeted therapies for KRAS-mutant non-small cell lung cancer (NSCLC). However, resistance eventually develops in nearly all patients. PanRAS(ON) inhibitors have emerged to avoid sotorasib resistance mechanisms, like the amplification of the KRAS(ON) conformation, the appearance of KRAS mutations other than G12C, and reactivation of other RAS isoforms.
- Other resistance mechanisms, including alterations in receptors tyrosine kinases (RTKs) and the induction of autophagy, can also be triggered by KRAS inhibitors. To study these mechanisms, we examined RTKs (e.g. MET) and autophagy induction (indicated by increased LC3-II conversion and SQSTM1/p62 degradation) as possible mechanisms of resistance to PanRAS(ON) inhibitors. We also examined whether these resistance mechanisms could be reversed with a MET inhibitor, ensartinib, or omeprazole (V-ATPase-Autophagy inhibitor), respectively.
- Study Goal:** To elucidate the efficacy of a novel Pan RAS (ON) inhibitor (RMC-6236 and GFH-276) in NSCLC cell lines and identify potential resistance pathways. To investigate drug combinations with V-ATPase inhibitors (omeprazole) or a MET inhibitor (ensartinib) to increase the effect of Pan RAS (ON) inhibitors and assess their potential benefits in overcoming identified resistance mechanisms in NSCLC.

METHODS



NSCLC cell lines: H358, H358R, H23, A549

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STATEMENT

All authors declare no potential conflicts of interest.

CONCLUSIONS

- Omeprazole pretreatment increased the antitumor effect of both Pan RAS (ON) inhibitors in a synergistic and additive way.
- Ensartinib cotreatment with both Pan RAS (ON) inhibitors increased the effect compared to drug monotherapy in a synergistic way.
- Pan RAS(ON) inhibitors were not able to maintain RTKs inactivated upon HGF stimulation, allowing possible early resistance responses through the activation of: EGFR, MET, MRAS, STAT3, AKT. Similar early resistance responses described with sotorasib. Omeprazole or ensartinib treatment in combination with both Pan RAS (ON) inhibitors reduced some of these protein responses.

RESULTS

