



Control/Tracking Number: 2025-RA-1573-WCLC

Fulzerasib, a KRAS-G12C inhibitor, has synergistic antitumor effect with omeprazole pretreatment in KRAS G12C NSCLC

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Introduction

Non-small cell lung cancer (NSCLC) harboring the KRAS G12C mutation poses a major challenge for effective and durable treatment. Fulzerasib (GFH925, IBI351), an irreversible KRAS G12C inhibitor, has demonstrated superior efficacy compared to sotorasib and adagrasib, achieving an objective response rate of 45.5% and a median progression-free survival of 9.6 months. Omeprazole, a proton pump inhibitor, has been shown to enhance cytoplasmic retention of cytotoxic drugs and sensitize cancer cells to chemotherapy and some target therapy, such as tepotinib. The current study aims to explore the antitumor effect and underlying mechanisms of fulzerasib in combination with omeprazole pretreatment in KRAS G12C-mutated NSCLC cell lines.

Methods

Three KRAS G12C-mutated NSCLC cell lines (H358, H23 and H2030) were selected to represent fulzerasib-sensitive, mildly resistant and resistant phenotypes, respectively. Cells were treated with varying doses of omeprazole pretreatment (administered 24 hours before fulzerasib) and subsequently treated with fulzerasib. Cell viability was assessed using MTT assays, and synergy was evaluated using Loewe, Bliss, HSA and ZIP models. Western blotting was performed to analyze the expressions of proteins and the regulations of pathways, including KRAS pathway, the MRAS-PP1c-SHOC2 complex, Met pathway, Wnt pathway, and markers like SLUG, HES1, and pEphA2.

Results

Synergistic effects of Fulzerasib and omeprazole pretreatment were observed across all models and cell lines. Combination treatment significantly reduced MRAS expression in the MRAS-PP1c-SHOC2 ternary complex. In cancer-related pathways, pMet and pAKT expression were markedly decreased, while MAPK pathway components (pRaf and pERK1/2) showed no significant changes. Wnt pathway analysis revealed decreased β -catenin expression without notable changes in pLRP6. SLUG, HES1 and pEphA2 expression were also significantly reduced.

Conclusions

This study highlights that fulzerasib exhibits synergistic antitumor effects with omeprazole pretreatment, potentially through the suppression of multiple cancer-related proteins and pathways. Future studies will explore additional mechanisms, including autophagy and ferroptosis, to further elucidate the therapeutic potential of this combination.