P2.023 Fulzerasib in combination with omeprazole pretreatment and/or terbinafine in KRAS G12C-mutant lung cancer cell lines

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INTRODUCTION

Therapeutic Challenge

KRAS G12C inhibitors have limited efficacy.

Fulzerasib, a new KRAS inhibitor

A novel agent with superior outcomes (ORR 49.1%, mPFS 9.7 months). Fulzerasib plus cetuximab, in a phase 1b/2 trial in patients with KRAS mutated NSCLC, showed encouraging activity[1,2].

Abnormal cholesterol metabolism in tumorigenesis

Squalene epoxidase (SQLE) serves as a rate-limiting enzyme in cholesterol metabolism.Terbinafine is a compound that inhibits SQLE expression[3].

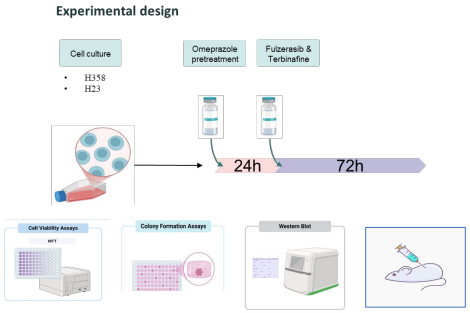
Proton pump inhibitor pretreatment

Omeprazole pretreatment decreases resistance to cytotoxic drugs[4].

Study Goal

To use terbinafine to enhance fulzerasib and omeprazole pretreatment through the modulation of key pathways involved in resistance to KRAS inhibitors.

METHODS



Three KRAS G12C-mutant NSCLC cell lines examined: H358,and H23, representing fulzerasib-sensitive to more resistant type.

Cells pretreated with omeprazole, followed by fulzerasib, with or without terbinafine.

Cell viability measured using MTT and colony formation assays. Western blot assay performed.

A subcutaneous model in BALB/c nude mice was inoculated with H358 cells. Mice allocated to eight treatment groups: control, fulzerasib, omeprazole, terbinafine, and combinations.

RESULTS

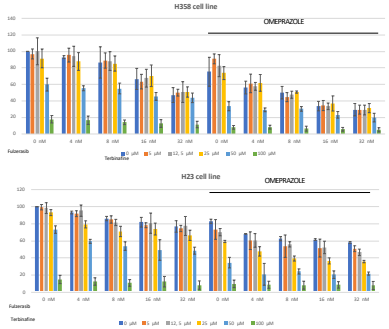


Figure 1. Dose-depenent cell viability inhibition with fulzerasib is potentiated by terbinafine and

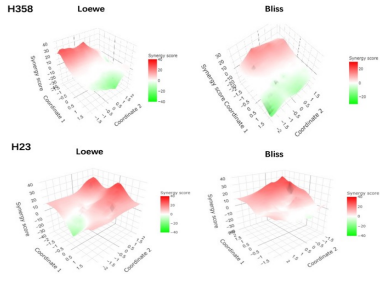


Figure 2. Fulzerasib synergizes with omeprazole pretreatment and terbinafine

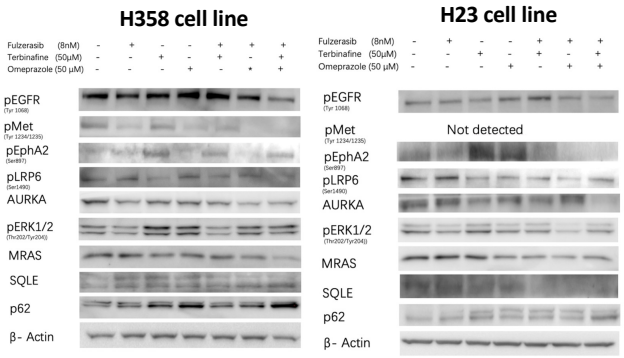


Figure 3. Omeprazole pretreatment combined with fulzerasib and terbinafine suppresses multiple signaling pathways

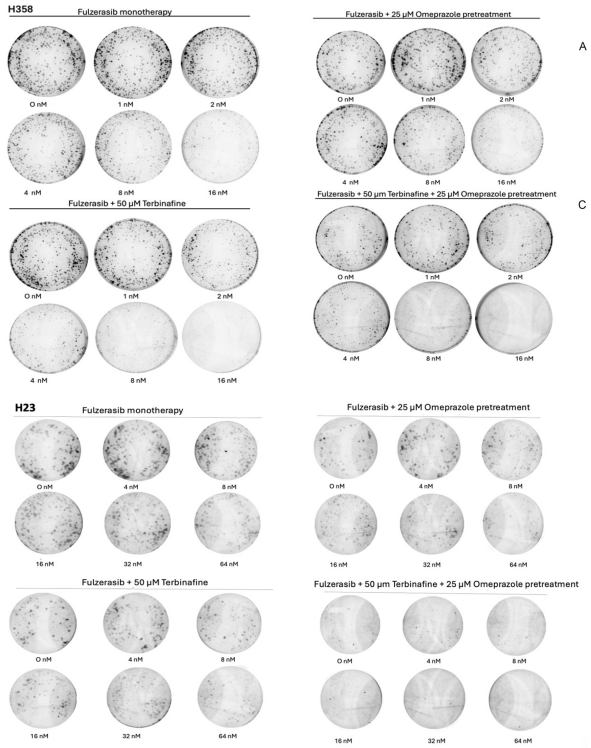


Figure 4. Omeprazole pretreatment combined terbinafine enhances the clonogenic inhibition of fulzerasib

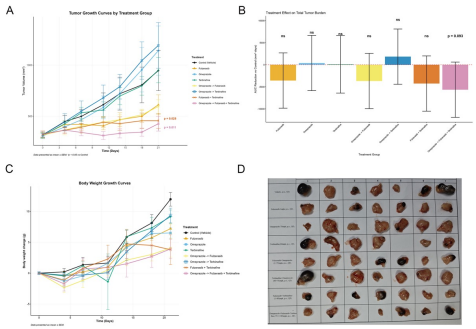


Figure 5. *In vivo* antitumor efficacy of omeprazole pretreatment and terbinafine in combination with fulzerasib in an H358 xenograft model

DISCUSSION AND CONCLUSION

Take Away Message

Modulation of SQLE expression synergizes with fulzerasib and omeprazole through signaling pathways related to KRAS inhibitor resistance.

Future Direction for Research

To study more extensively the mechanism of action of the triple-drug combination by investigating autophagy, lipid metabolism, cell death processes (apoptosis, necrosis, ferroptosis), and the cell cycle.

The triple combination of omeprazole pretreatment and terbinafine could improve the efficacy of the KRAS inhibitor fulzerasib and delay the development of resistance.

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