

INTRODUCTION

Therapeutic Challenge

- KRAS G12C-mutant NSCLC shows limited clinical response to sotorasib due to intrinsic and acquired resistance. Selinexor, a selective XPO1 inhibitor, also faces intrinsic resistance in certain KRAS-mutant models.

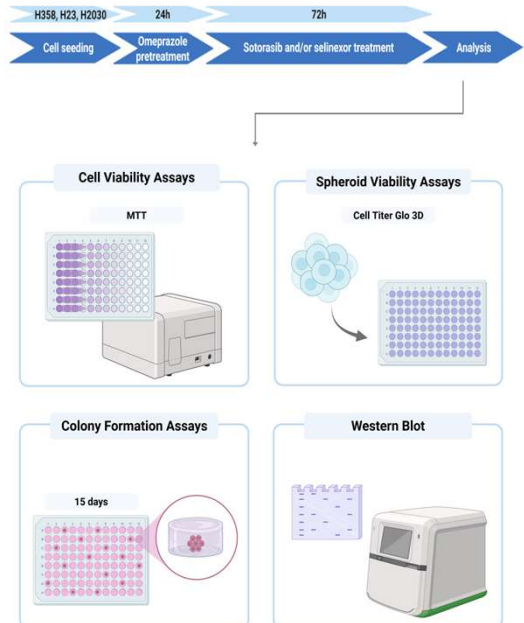
Rationale

- Omeprazole, a V-ATPase inhibitor, enhances cytoplasmic drug retention when used as a pretreatment, improving sensitivity to specific targeted therapies.

Study Goal

- Evaluate whether omeprazole pretreatment enhances efficacy and reverts resistance to sotorasib or selinexor in KRAS G12C-mutant NSCLC. Investigate underlying mechanisms of drug synergy.

METHODS



RESULTS

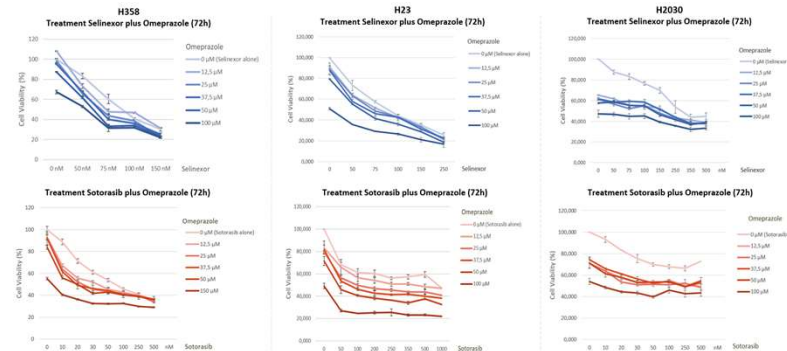


Figure 1. Omeprazole pretreatment enhances sensitivity of KRAS G12C-mutant NSCLC cell lines to sotorasib and selinexor. Dose-response curves for sotorasib and selinexor ± omeprazole in H358 (sensitive to both drugs), H23 (resistant to sotorasib), and H2030 (resistant to both).

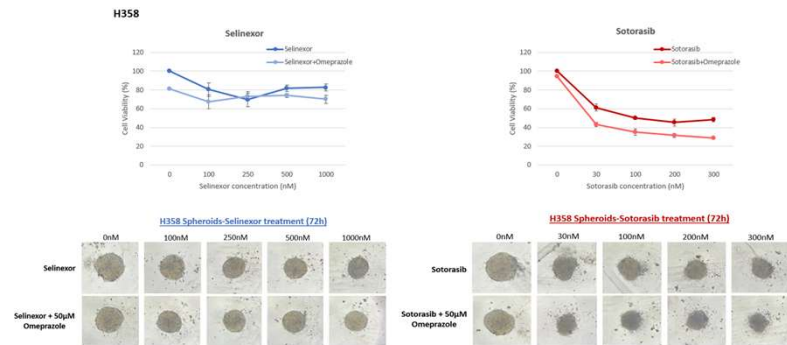


Figure 2. Omeprazole pretreatment potentiates the efficacy of sotorasib and selinexor in 3D KRAS G12C-mutant NSCLC spheroid-models. Dose-response curves for sotorasib and selinexor ± omeprazole in H358-derived spheroids. Representative bright-field images illustrate treatment-induced morphological changes.

DISCUSSION AND CONCLUSION

Take Away Message

- This study highlights the role of omeprazole pretreatment as a strategy to enhance sotorasib and selinexor efficacy and, moreover, to reverse resistance in 2D and 3D KRASG12C-mutant NSCLC models through the inhibition of multiple resistance pathways and the blocking of autophagy.

Future Direction for Research

- Comprehensive *in vivo* studies are crucial to clarify the therapeutic potential of these combinations. CAM models are under development, with planned extension to murine studies to validate clinical relevance.

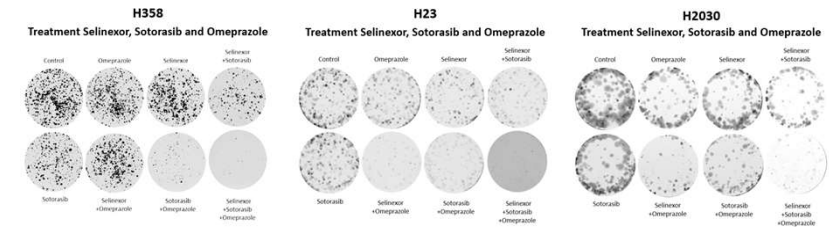


Figure 3. Omeprazole pretreatment enhanced the clonogenic suppression induced by sotorasib or selinexor in KRASG12C-mutant NSCLC cell lines. Representative images of crystal violet-stained colonies formed by H358, H23, and H2030 cells.

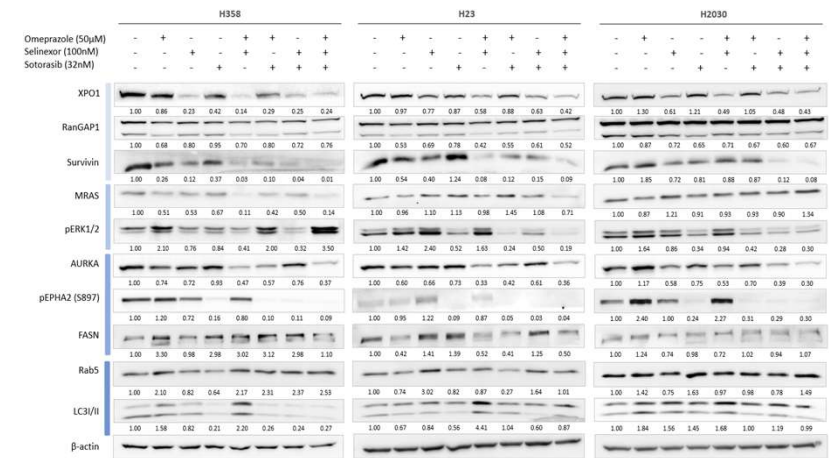


Figure 4. Omeprazole potentiates sotorasib/selinexor activity by blocking resistance pathways and autophagy in KRASG12C-mutant NSCLC cell lines. Western blot analysis in H358, H23, and H2030 cell lines. Proteins are grouped and color-coded according to function: resistance-related signaling proteins—including XPO1-associated, RAS/MAPK pathway, and other markers—and autophagy-related proteins.

REFERENCES & ACKNOWLEDGEMENTS

Key References

- Khan HY, Nagasaka M, Li J, et al. Inhibitor of the Nuclear Transport Protein XPO1 enhances the anticancer efficacy of KRAS G12C inhibitors in preclinical models of KRAS G12C-mutant cancers. *Cancer Res Commun.* 2022 May;2(5):342-352.
- Rosell R, Jantus-Lewintre E, Cao P, Cai X, Xing, B, et al. KRAS-mutant non-small cell lung cancer (NSCLC) therapy based on tepotinib and omeprazole combination. *Cell Commun Signal.* 2024 Jun 12;22(1):324.