

P2.02.39: Fulzerasib, a KRAS-G12C inhibitor, has synergistic antitumor effect with omeprazole pretreatment in KRAS G12C NSCLC

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INTRODUCTION

Therapeutic Challenge

- Current KRAS G12C inhibitors exhibit suboptimal efficacy and required resistance¹.

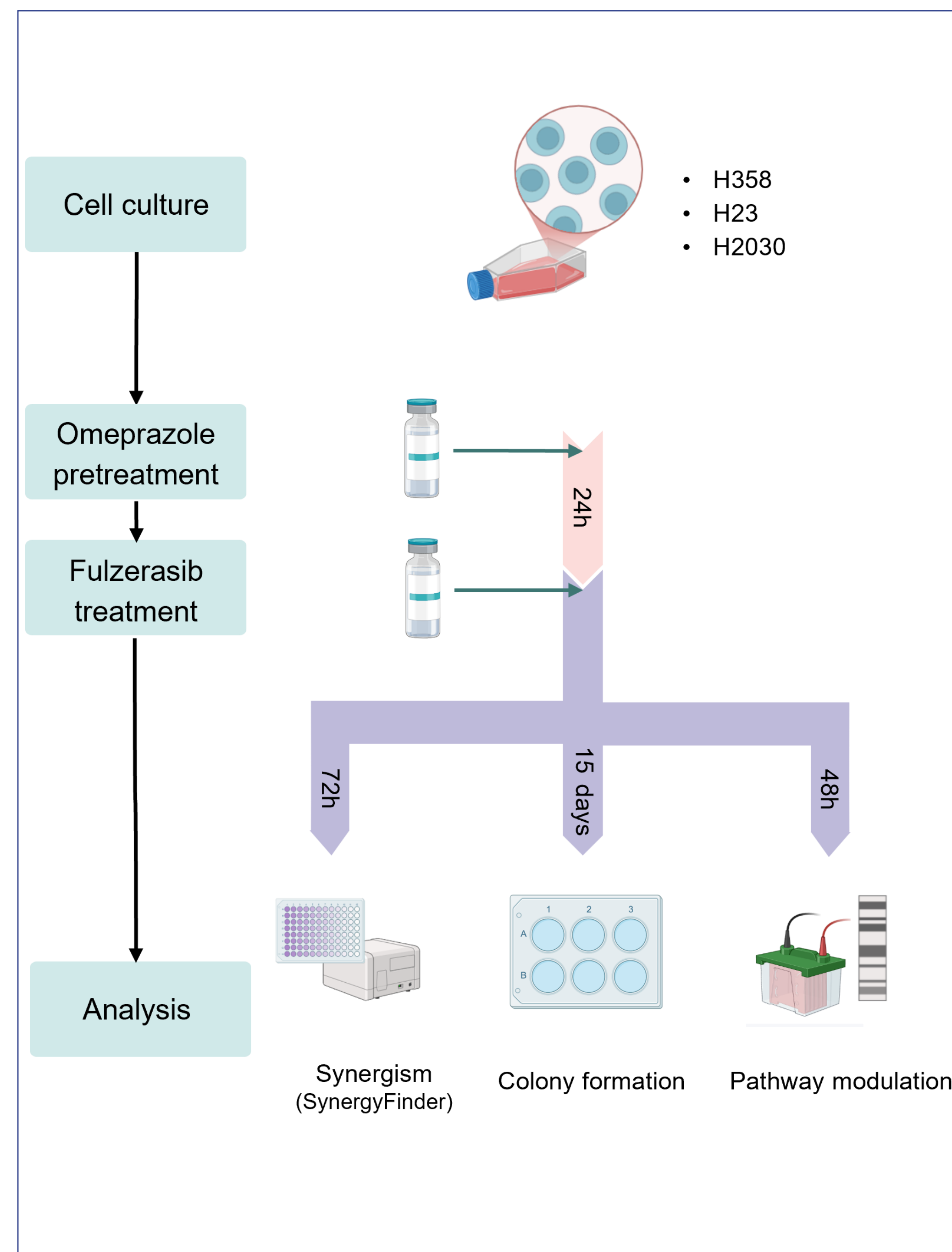
Fulzerasib Advantage

- Novel agent with promising outcomes (ORR 49.1%, mPFS 9.7 months)¹.

Study Goal

- Exploit omeprazole pretreatment to enhance fulzerasib efficacy through pathway modulation².

METHODS



RESULTS

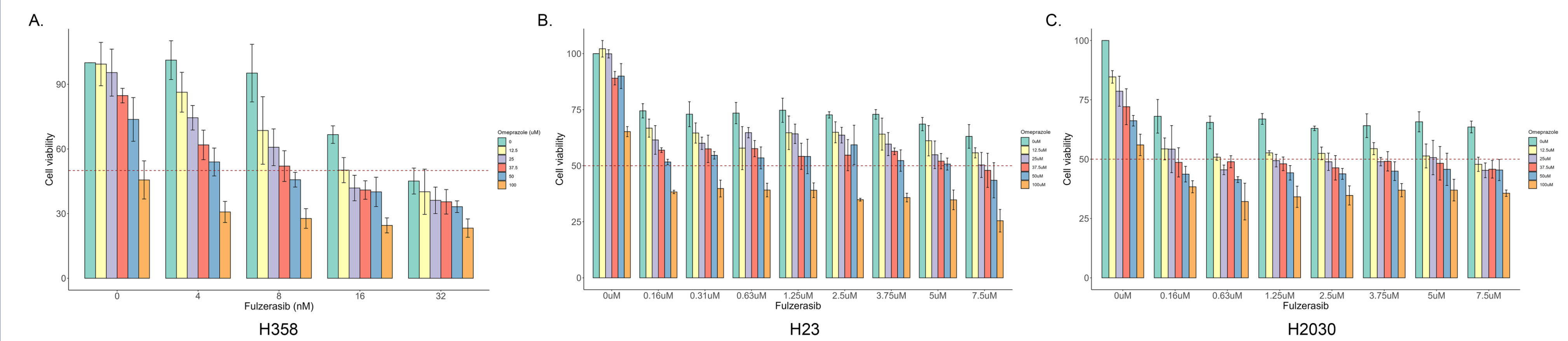


Figure 1. Omeprazole pretreatment enhances fulzerasib efficacy. Dose-dependent viability reduction with fulzerasib is potentiated by omeprazole pretreatment.

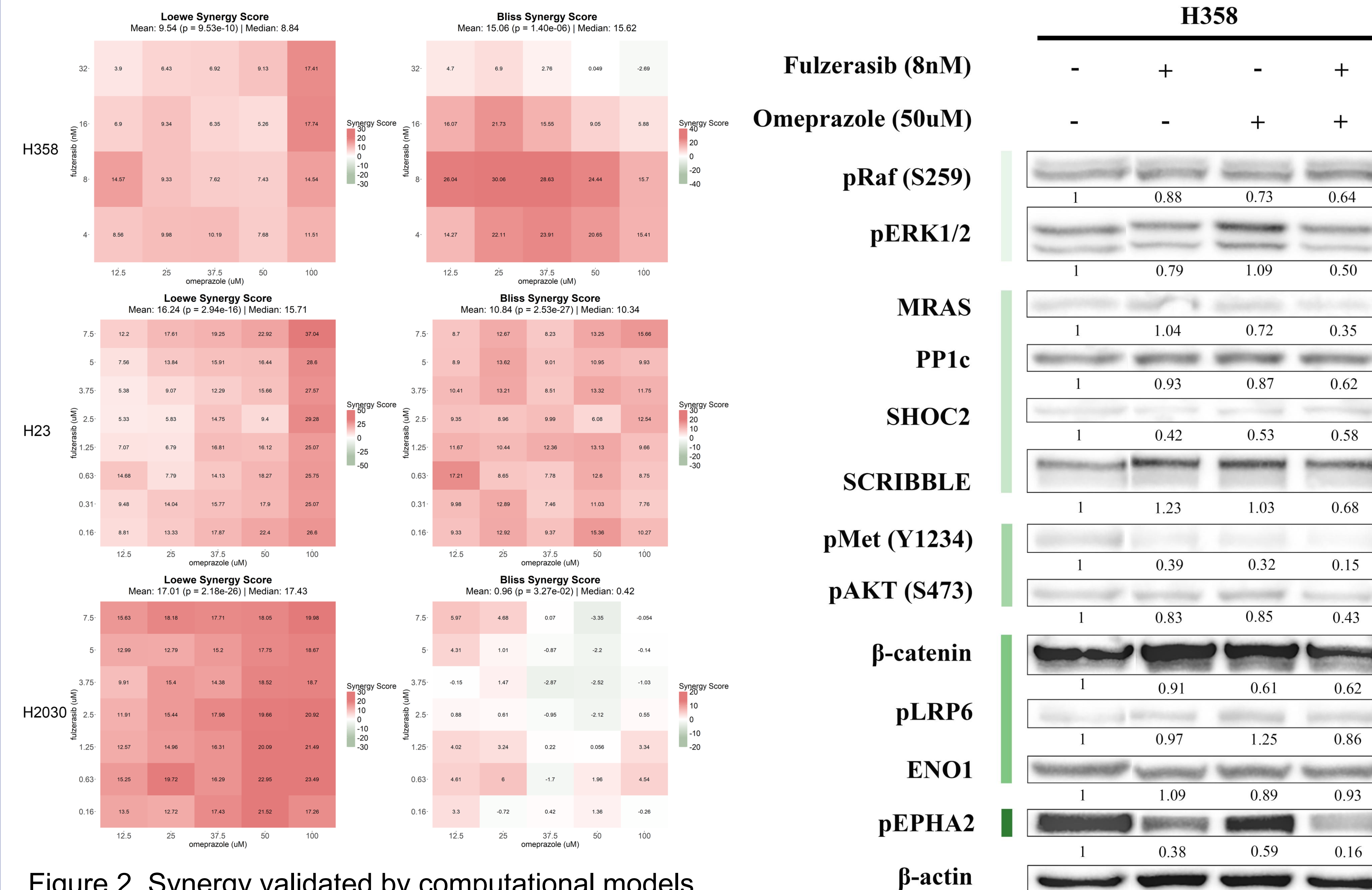


Figure 2. Synergy validated by computational models. Dose-matrix heatmaps show enhanced synergy zones (red) with omeprazole pretreatment combination.

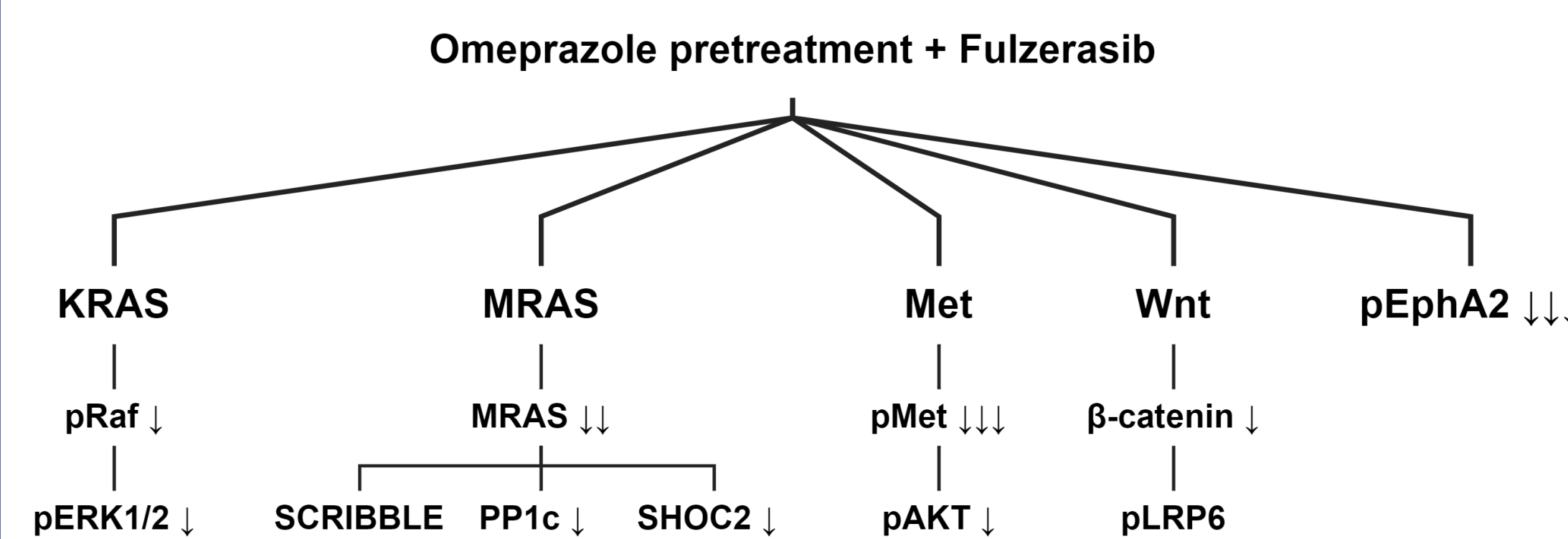


Figure 3. Fulzerasib combined with omeprazole pretreatment suppresses multiple pathways. Western blotting results indicated MRAS-PP1c-SHOC2 complex/ pMet/ pAKT and pEphA2 expression levels were downregulated by the combination.

Figure 4. Pathway modulation by Fulzerasib + Omeprazole pretreatment. Arrows indicate activation (↑) or suppression (↓) of key proteins in Figure 3.

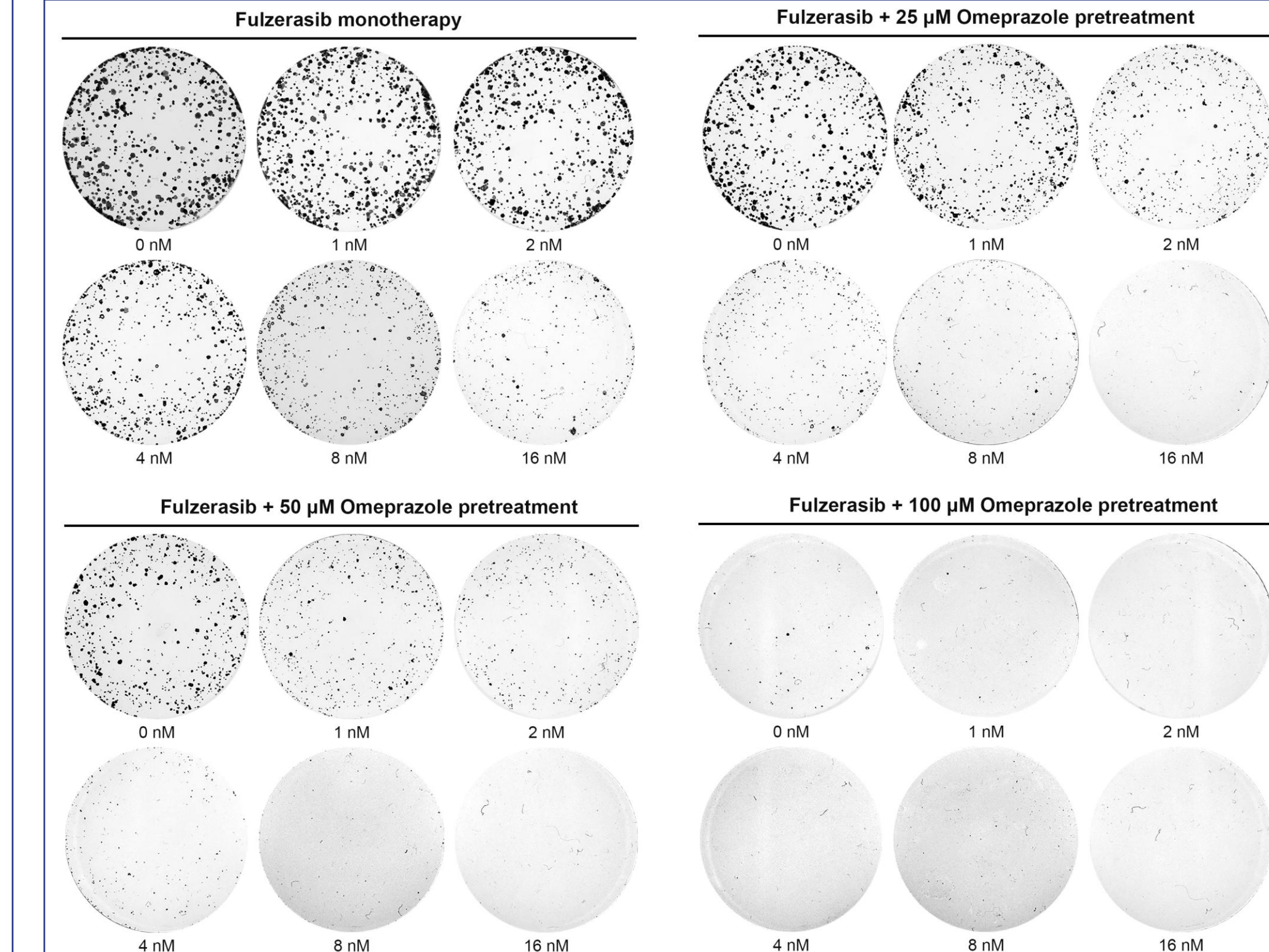


Figure 5. Omeprazole pretreatment enhances Fulzerasib's effect in inhibiting colony formation. Omeprazole pretreatment (0, 25, 50, 100 uM, 24h) → Fulzerasib dose-gradient (0-16 nM, below each well) in H358

DISCUSSION AND CONCLUSION

Take Away Message

- Omeprazole pretreatment synergizes with fulzerasib via multi-pathway suppression

Clinical Expectation

- (Pre) Omeprazole might enhance fulzerasib efficacy and delay resistance.

Future Exploration

- In vivo validation
- Mechanistic expansion

REFERENCES & ACKNOWLEDGEMENTS

Key References

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