

P2.046: V-ATPase Inhibitor Enhances the Effect of Tepotinib (c-Met Inhibitor) and RMC-6236 (Pan-Ras(ON) Inhibitor) in KRAS-Mutant NSCLC

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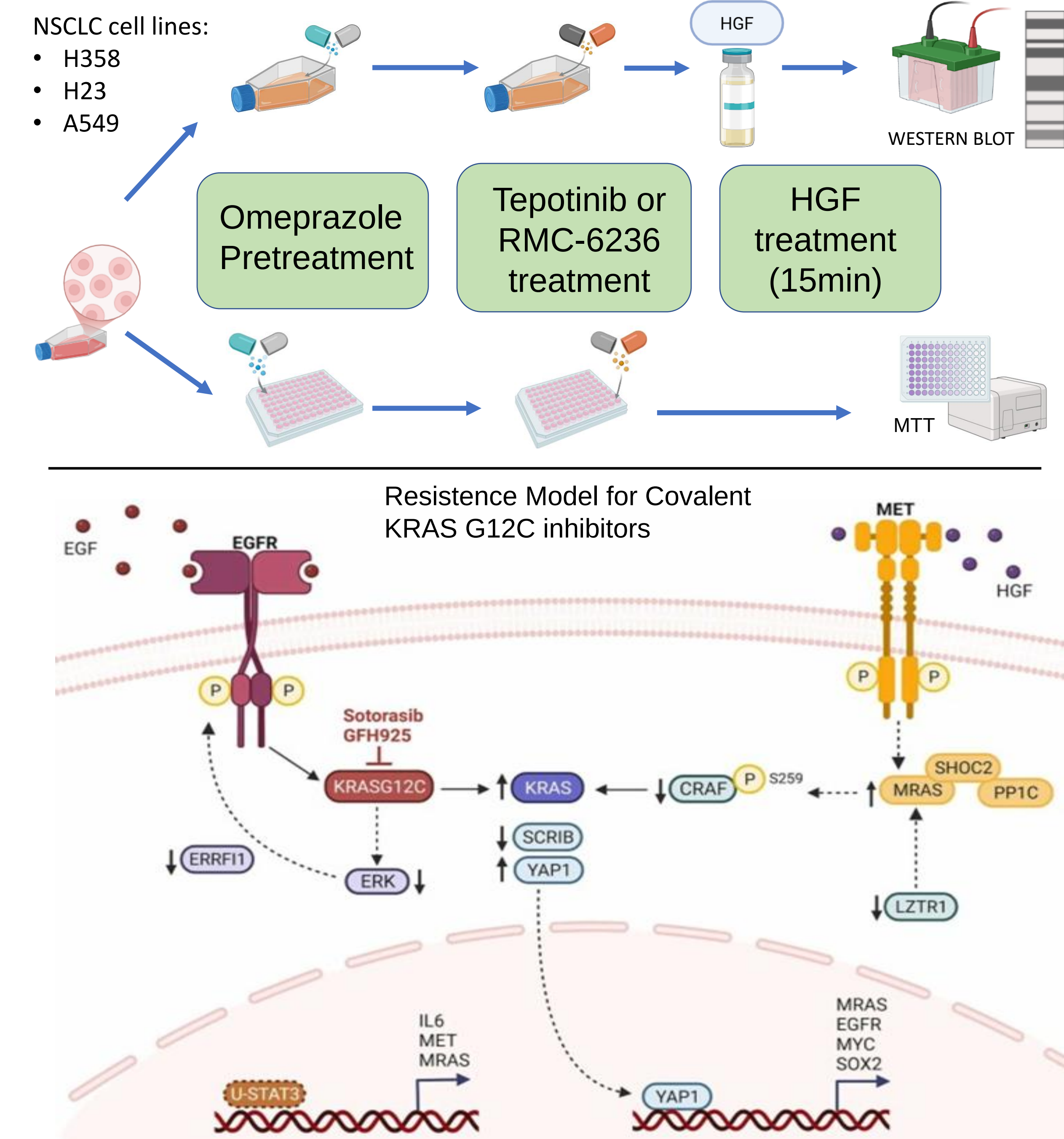
INTRODUCTION

- The FDA approved KRAS G12C inhibitors (Sotorasib and Adragrasib) both exhibit low efficacy (Approximately 40% ORR) and end up causing acquired resistance [1].
- Early adaptive resistance to Sotorasib includes the activation of EGFR, MET and the MRAS:SHOC2:PP1C trimeric complex [2].
- Dr Rosell lab previously demonstrated that Omeprazole pretreatment was able to increase the antitumor effect of Tepotinib [1].

Study Goal

The current objective of this project is to gain a deeper understanding of the molecular mechanisms of action using Tepotinib in combination with Omeprazole. Also, to investigate the effects and mechanisms of action, when combining Omeprazole with RMC-6236, a new PAN RAS On inhibitor [3].

METHODS



REFERENCES

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- J. Jiang et al., "Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers," *Cancer Discov*, vol. 14, no. 6, pp. 994–1017, Jun. 2024, doi: 10.1158/2159-8290.CD-24-0027.
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RESULTS

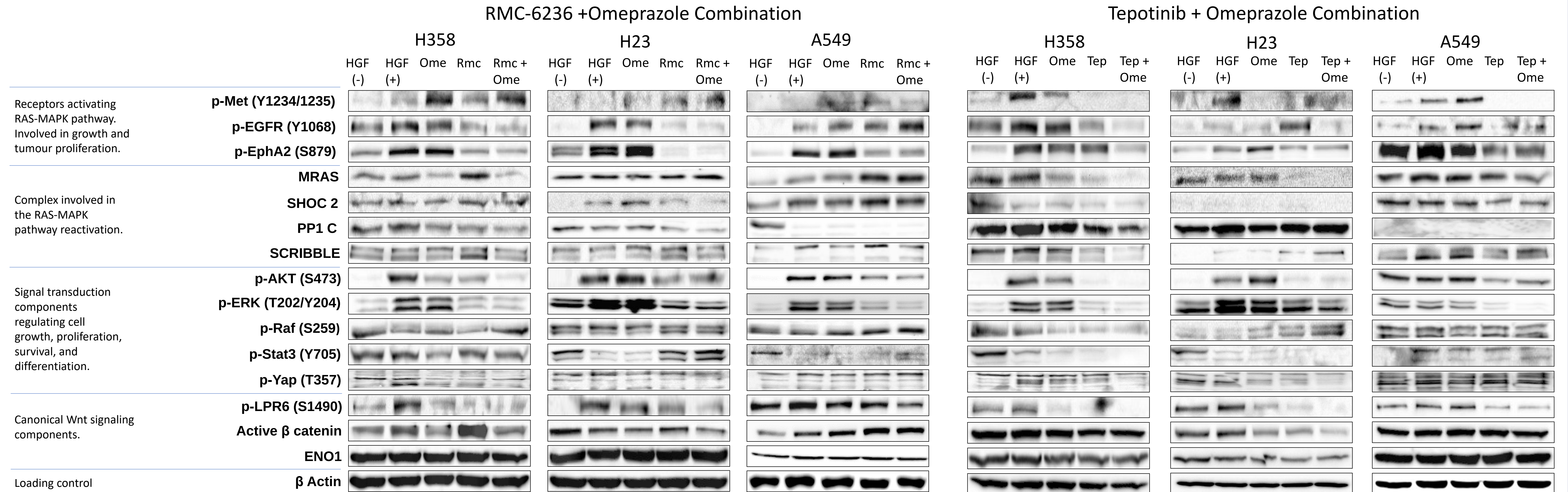


Figure 1. Effect of RMC-6236 or Tepotinib monotherapy and the respective combinations with omeprazole in the activation and expression of proteins related to RAS-MAPK and WNT pathways. Western blot analysis show protein levels in H358, H23 and A549 NSCLC cell lines cultured in starving conditions (0.5% FBS) and single treated with (RMC-6236 20 nM, Tepotinib 10 μ M, Omeprazole 100 μ M) or the combinations. Before extract collection, all groups, except control, here treated with HGF (30 ng/ml) for 15 minutes. Protein extracts were taken at 24 h after RMC-6236 or Tepotinib treatment. β -actin was used as loading control.

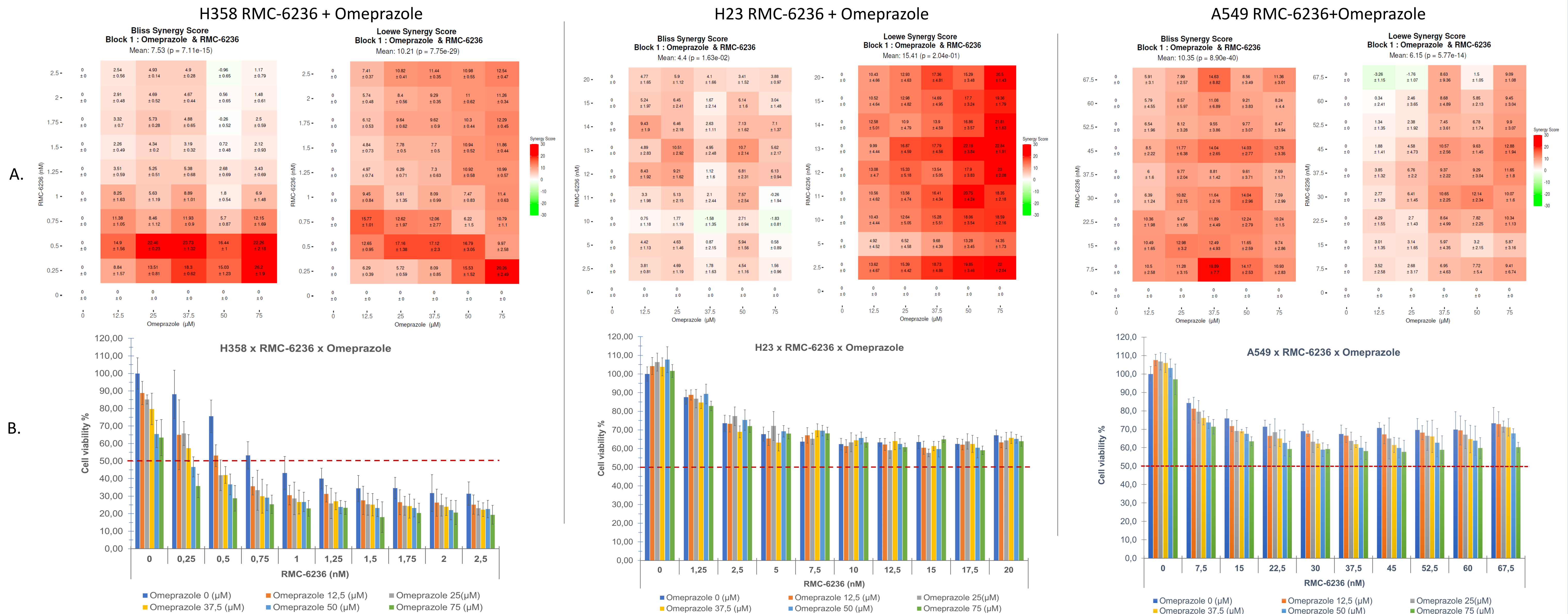


Figure 2. (A) RMC-6236 and Omeprazole Synergistic analysis represented in heatmap plots. By MTT, the viability effect of different doses combination of RMC-6236 and Omeprazole was quantified in H358, H23 and A549 NSCLC cell lines. Data was analysed by Computational software Synergy Finder+ [4] for Bliss and Loewe models. Red indicates a Synergistic effect for the combination. Colour intensity indicates greater synergism. (B) Graphs representing cellular viability. Cell lines were treated with RMC-6236 and Omeprazole, alone or in combination. Each group of bars indicates the dose of RMC-6236 while the color of the bars indicates Omeprazole doses.

CONCLUSIONS

- Omeprazole Pretreatment increased the antitumor effect of both Tepotinib (c-Met inhibitor) and RMC-6236 (PAN RAS on inhibitor).
- In most cell lines, the combination of Omeprazole and Tepotinib is more efficient in reducing cancer-related pathways than Tepotinib alone.
- In some cell lines, RMC-6236 alone activates early resistance mechanisms similar to those observed with Sotorasib. The Omeprazole and RMC-6236 combination reverts this response, decreasing YAP1 and several receptors tyrosine kinase activation, and MRAS expression.