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MET or SHP2 inhibition enhances targeted therapies and delays the emergence of resistance in oncogene-driven NSCLC

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BACKGROUND

Despite advancements made in available targeted therapies for non-small cell lung cancer (NSCLC), most patients have an incomplete response and eventually acquire resistance. It is well known that MET signaling is a key pathway that mediates osimertinib resistance[1]. Resistance could be prevented or delayed by concurrently targeting multiple proteins in critical signaling pathways, including the MET receptor or SHP2, a key node downstream of receptor kinases[2]. Here, we explore the concept of combining upfront targeted therapies with a selective MET inhibitor (tepotinib) or SHP2 inhibitor (TNO155) as promising therapeutic strategies for oncogene-driven NSCLC.

METHODS

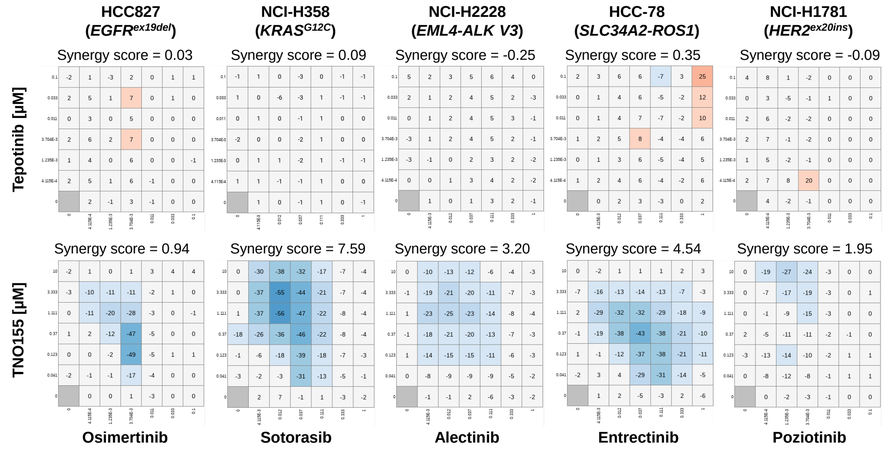
All NSCLC cell lines were obtained from commercial vendors. Drugs were synthesized at the healthcare business of Merck KGaA, Darmstadt, Germany, or purchased from commercial vendors. Cell viability upon inhibitor treatment was investigated by Resazurin Cell Viability Assay (R&D Systems), and the effect of the inhibitors on colony forming ability was assessed. Western blot was conducted to analyze pathway activity. The emergence of resistance was investigated by measuring the cell surface confluence using the IncuCyte S3 system (Essen Bioscience).

Molecular NSCLC subtype	Cell line	Targeted therapy	Combination tested
EGFR ex19del	HCC827	Osimertinib	+ TNO155 + Tepotinib
KRAS G12C	NCI-H358	Sotorasib	+ TNO155 + Tepotinib
EML4-ALK (V3)	NCI-H2228	Alectinib	+ TNO155 + Tepotinib
SLC34A2-ROS1	HCC-78	Entrectinib	+ TNO155 + Tepotinib
HER2 ex20ins	NCI-H1781	Poziotinib	+ TNO155 + Tepotinib

Table 1: Summary of used NSCLC cell lines with their respective targeted therapies and tested combinations.

RESULTS

I. Tepotinib does not further sensitize already sensitive cells to targeted therapies, but synergism occurs when drugs are combined with TNO155



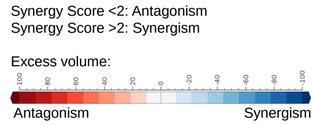


Figure 1: Antiproliferative effects were assessed using combination dose matrices in 6-day viability assays. One representative Loewe excess matrix as well as the mean synergy scores of three independent experiments are shown.

II. Tepotinib does not further sensitize already sensitive cells to targeted therapies, but colonies are reduced when drugs are combined with TNO155

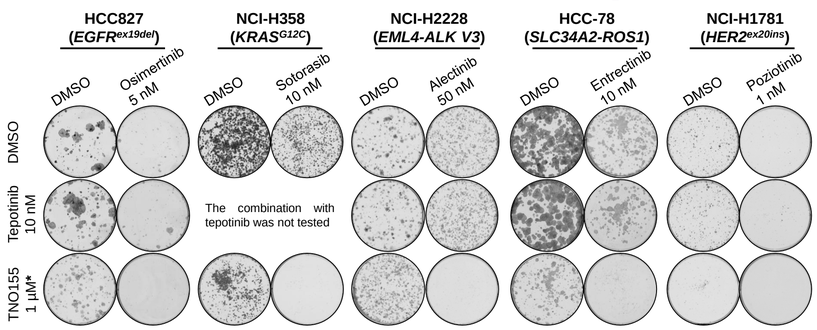


Figure 2: Antiproliferative effects were assessed in colony formation assays lasting 2 weeks.

*In HCC-78 100 nM TNO155 has been applied.

RESULTS

III. Combining alectinib with TNO155 leads to stronger ERK signaling abrogation than single therapies

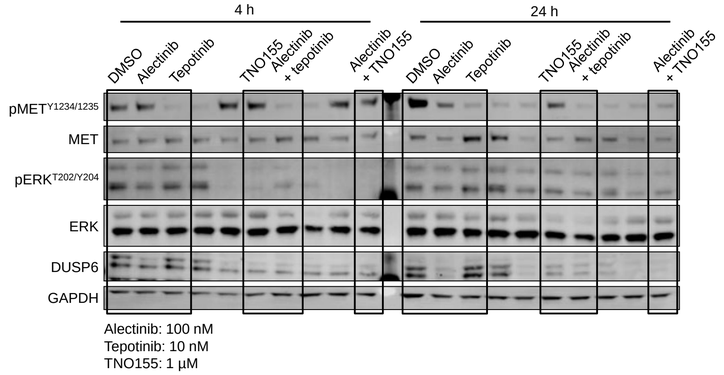


Figure 3: ERK pathway analysis has been performed in NCI-H2228 cell lysates by Western blot with the indicated antibodies. Similar results were obtained with the other tested cell lines. Lanes that are not marked by boxes correspond to treatments not relevant for this study.

IV. Combining osimertinib with tepotinib delays the emergence of osimertinib resistance in HCC827 cells that have high MET protein expression and phosphorylation

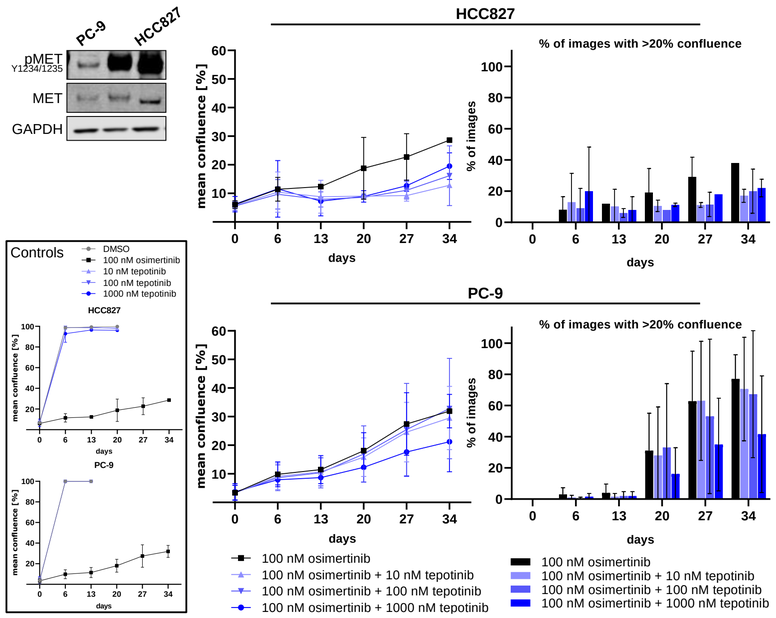


Figure 4: Cells have been seeded at ~5% of seeding density. Cell surface confluence was measured by analyzing 50 images weekly. N = 2; mean ± SD.

V. In HCC827 cells, combination treatment decreases EGFR-, MET- and downstream signaling more potently than osimertinib alone

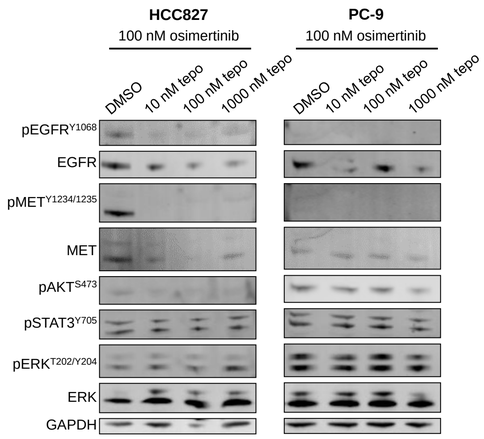
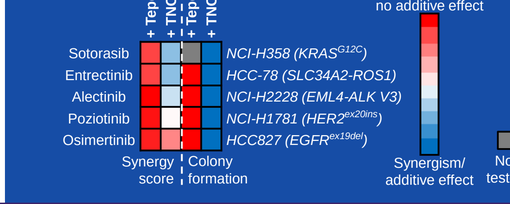


Figure 5: Western blot analysis with the indicated antibodies at day 34. In HCC827 cells, osimertinib + tepotinib decreased the phosphorylation of EGFR, MET and AKT more potently than osimertinib alone, indicating stronger inhibition of the signaling pathways.

CONCLUSIONS

Our data show that combining targeted therapies with an SHP2 inhibitor synergistically decreases the viability of oncogene-driven NSCLC cell lines, indicating that initial combination therapy may be an appealing approach to improve patient outcomes. The observed delay in the emergence of osimertinib resistance, when combining a MET inhibitor with osimertinib, provides preclinical evidence to further support investigating MET inhibition upfront to improve the long-term therapeutic efficacy of EGFR inhibitors.



References

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2. Pudelko, L. *et al.* (2020). SHP2 Inhibition Influences Therapeutic Response to Tepotinib in Tumors with MET Alterations. iScience *23*, 101832.

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