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Summary

BIOMARKER-DRIVEN VERTICAL BLOCKADE OF THE NEDDYLATION–BIRC5 AXIS: A PRECISION MEDICINE STRATEGY FOR TP53-DEFICIENT GASTRIC CANCER

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Preclinical study identifies TP53 functional status as a candidate predictive biomarker for dual neddylation–BIRC5 inhibition in gastric cancer, with TP53-deficient patient-derived organoids showing greatest response to combined MLN4924 and BIRC5 inhibitor.

KEY POINTS

- In TP53-null KATO-III gastric cancer cells, the NAE1 inhibitor MLN4924 induced apoptosis but paradoxically up-regulated the anti-apoptotic protein BIRC5, a feedback escape mechanism likely underlying clinical resistance to NAE1 inhibition.
- Co-targeting with a selective BIRC5 inhibitor abrogated this adaptive response and produced significant, supra-additive apoptotic cell death, demonstrating clear pharmacological synergy in TP53-null cells.
- TP53-proficient SNU-1 cells were intrinsically sensitive to MLN4924 monotherapy and derived no benefit from BIRC5 inhibition, confirming a TP53-dependent therapeutic vulnerability.
- The TP53-stratified efficacy pattern was fully recapitulated in patient-derived gastric cancer organoids, with TP53-deficient organoids showing the greatest response to the combination.
- TP53 functional status emerged as a candidate predictive biomarker for patient selection, and PDO-based pharmacotyping offers a feasible platform for prospective stratification.
- The findings warrant clinical translation through a biomarker-enriched early-phase trial in TP53-deficient gastric cancer, a high-need population for which no approved targeted therapy exists.

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