

P2.046: Targeting MCL-1 Overcomes Adaptive Resistance to PI3K Inhibition in Thymic Carcinoma

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INTRODUCTION

- Thymic carcinoma is a rare malignancy with a poor prognosis, and treatment options for advanced disease remain limited¹.
- The PI3K/AKT signaling pathway regulates cell proliferation and metabolism, making it a potential therapeutic target in multiple malignancies, including thymic carcinoma (TC)².
- The pan-PI3K inhibitor buparlisib shows modest activity in a phase II trial of relapsed or refractory thymoma; however, its single-agent activity was limited, with a median progression-free survival of 11.1 months².
- The mechanisms of resistance to buparlisib remain unclear, underscoring the need for combination strategies to overcome it.

1) Mediastinum. 2024;8:36.

2) Front Oncol. 2022;12:891383.

METHODS

Cell lines and reagents

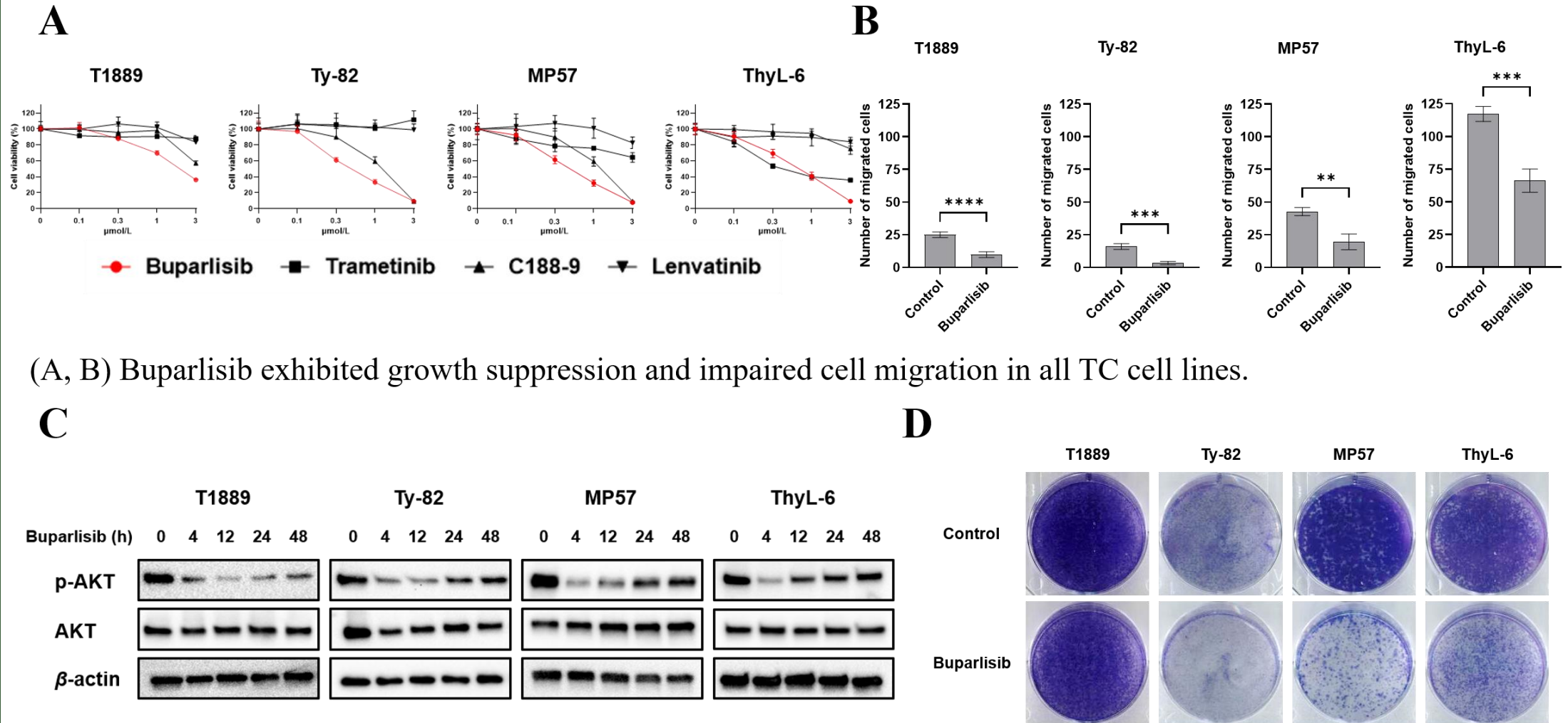
- Four human thymic carcinoma cell lines (T1889, Ty-82, MP57, and ThyL-6) were used.
- Buparlisib (PI3K inhibitor), Trametinib (MEK inhibitor), C188-9 (STAT3 inhibitor), Lenvatinib (VEGFR inhibitor), and S63845 (MCL-1 inhibitor) were used.

Statistical analysis

- Statistical significance was determined using one-way analysis of variance (ANOVA), two-way ANOVA, or unpaired t-tests. $P < 0.05$ was considered statistically significant.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$; ns, not significant.

Role of PI3K/AKT survival signaling in thymic carcinoma cells



(A, B) Buparlisib exhibited growth suppression and impaired cell migration in all TC cell lines.

C

D

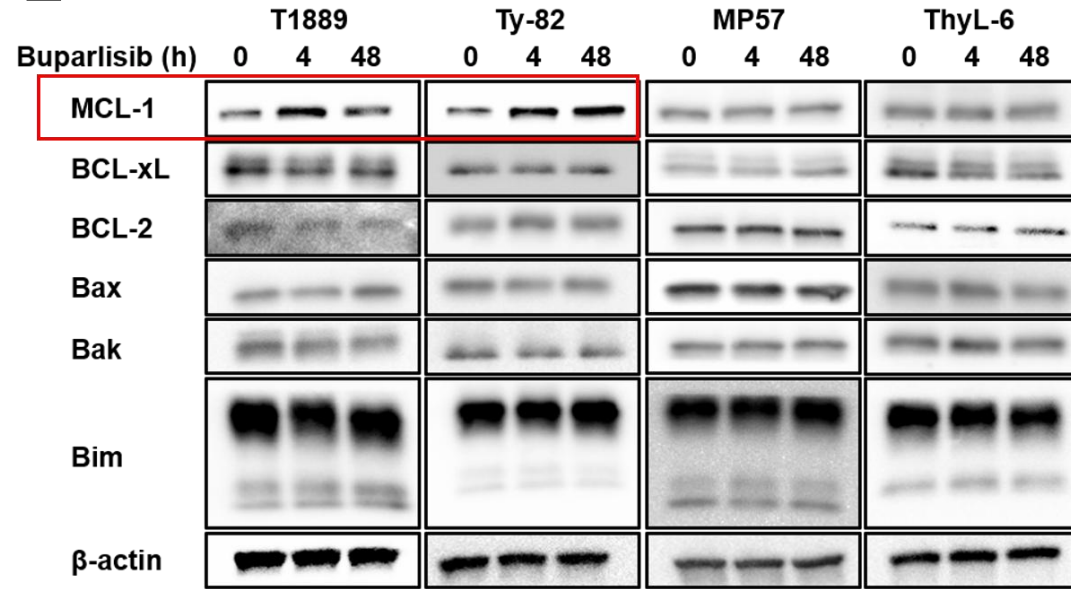
(C) Buparlisib transiently suppressed AKT phosphorylation, which reactivated by 48 h in all TC cell lines.

(D) Subpopulation of cells survived prolonged exposure for 9 days in all TC cell lines.

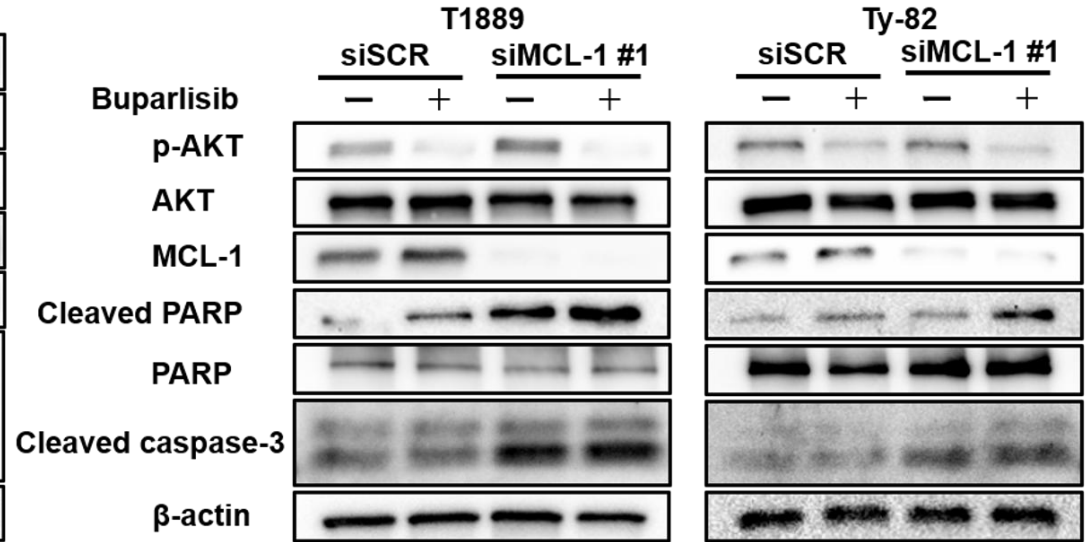
⇒ These findings suggest that TC cells adapt to PI3K inhibition despite its cytostatic and anti-migratory effects.

MCL-1 upregulation mediates adaptive resistance to PI3K inhibition

E



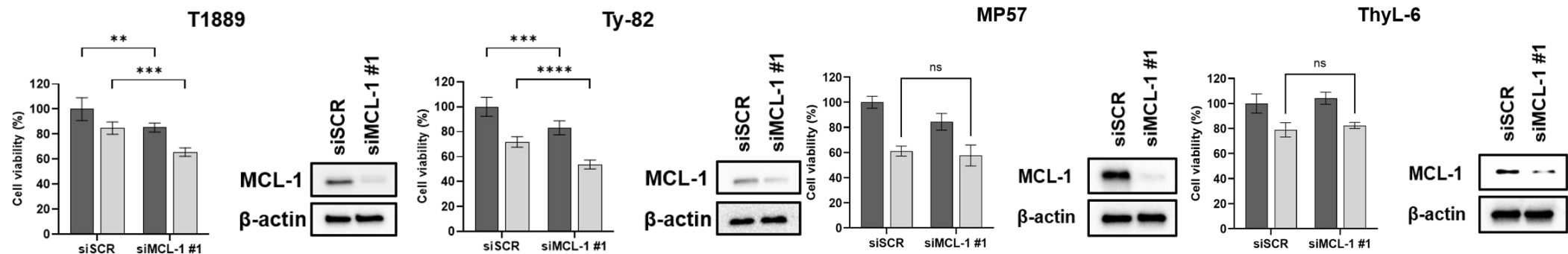
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(E) Upregulation of the anti-apoptotic protein MCL-1 following buparlisib in T1889 and Ty-82 cell lines.

(G) MCL-1 knockdown in combination with buparlisib increased the expression of apoptotic proteins.

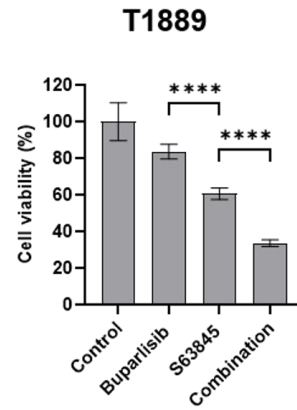
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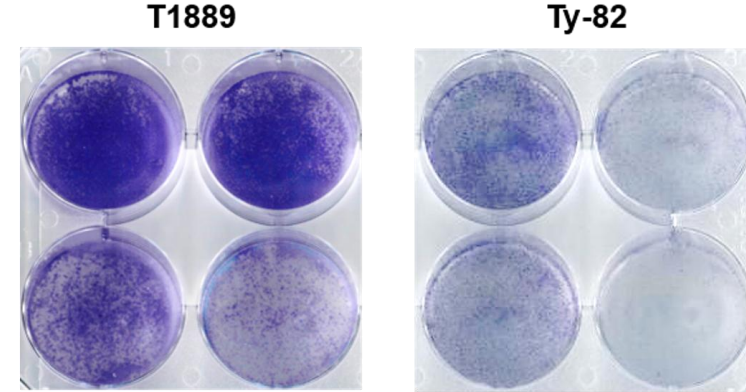
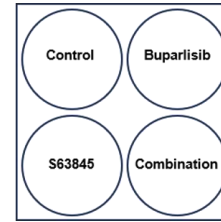
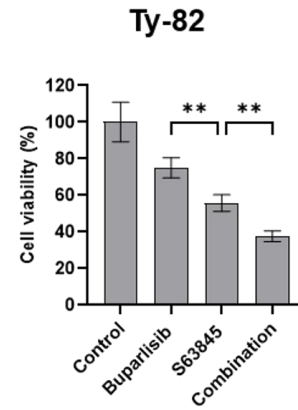
(F) MCL-1 knockdown enhanced the effect of buparlisib in T1889 and Ty-82 cells showing MCL-1 upregulation.

Combination effect of PI3K and MCL-1 inhibitors in thymic carcinoma cells

H

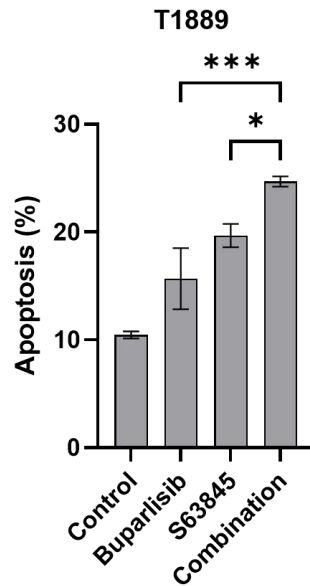


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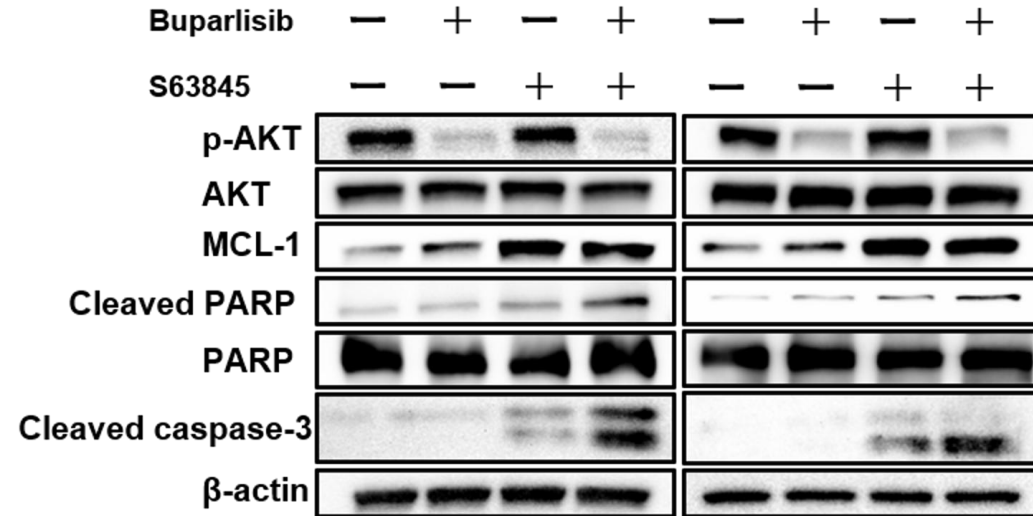
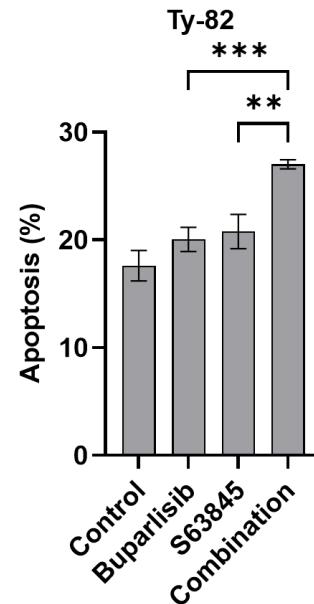


(H, I) Combined inhibition of PI3K and MCL-1 enhanced antiproliferative activity.

J

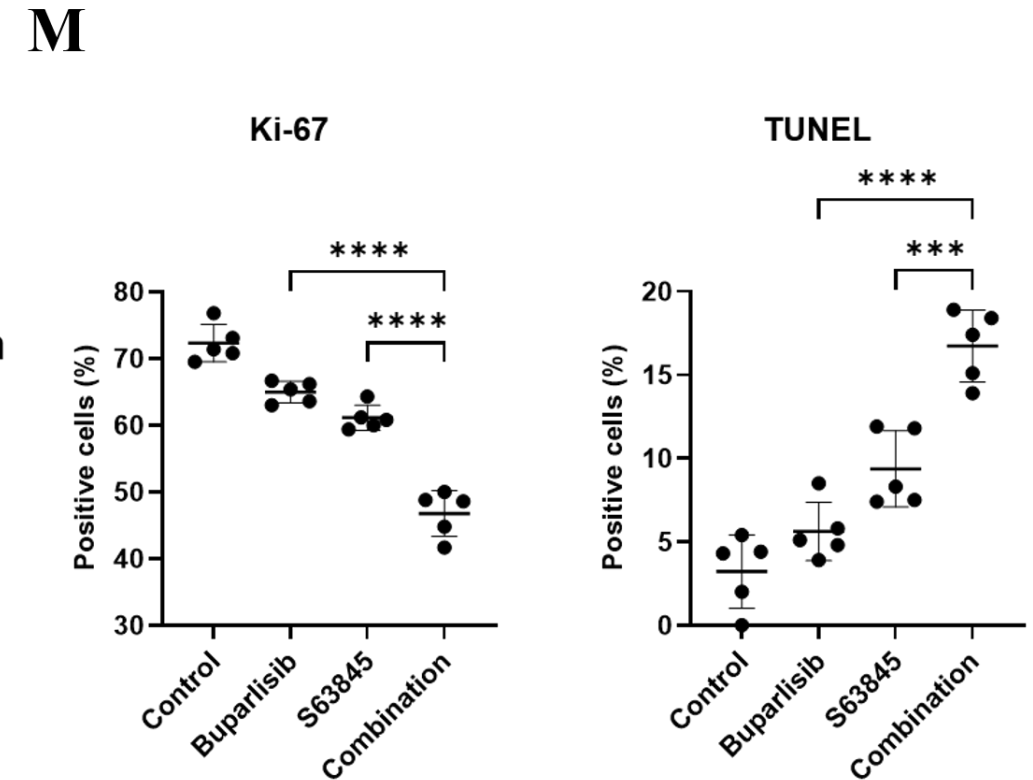
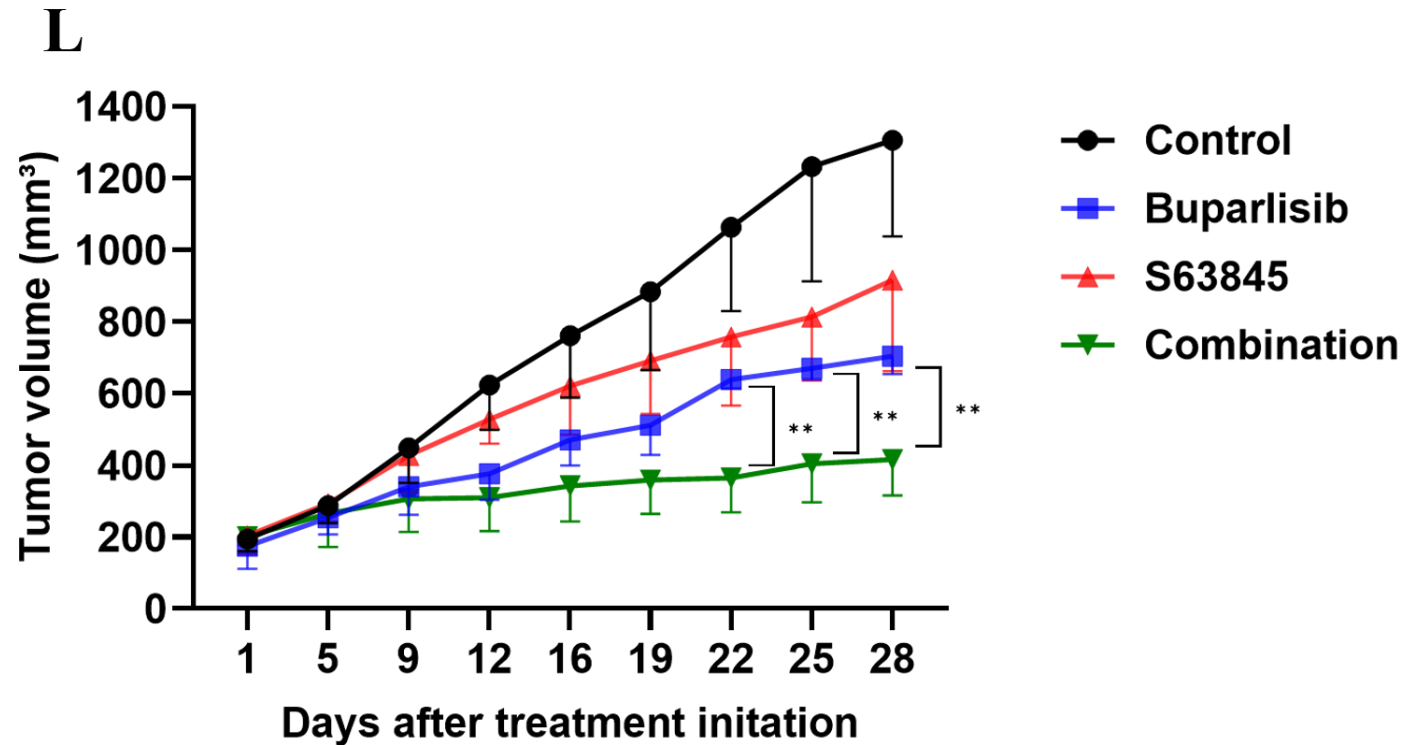


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(J, K) Combined inhibition of PI3K and MCL-1 enhanced apoptosis.

Combination of PI3K and MCL-1 inhibitors delays tumor growth



(L) Combination therapy significantly inhibited tumor progression.

(M) Combination therapy reduced Ki-67 positivity and increased TUNEL-positive cells compared with monotherapy.

DISCUSSION AND CONCLUSION

- PI3K inhibition showed predominantly cytostatic effects in TC cells, while adaptive MCL-1 upregulation contributed to resistance to PI3K inhibition in a subset of TC models.
- Combined PI3K and MCL-1 inhibition enhanced antitumor activity and apoptotic cell death in TC models exhibiting adaptive MCL-1 induction.
- Clinical translation of this combination strategy will require reliable predictive biomarkers and careful evaluation of potential toxicities.

DISCLOSURE

COI Disclosure: No relevant financial relationships to disclose.

Artificial Intelligence (AI) Use Disclosure:

ChatGPT was used to assist with language editing and layout of this poster.

All experimental data, analyses, and interpretations were generated and verified by the authors, who take full responsibility for the accuracy and integrity of the content.