

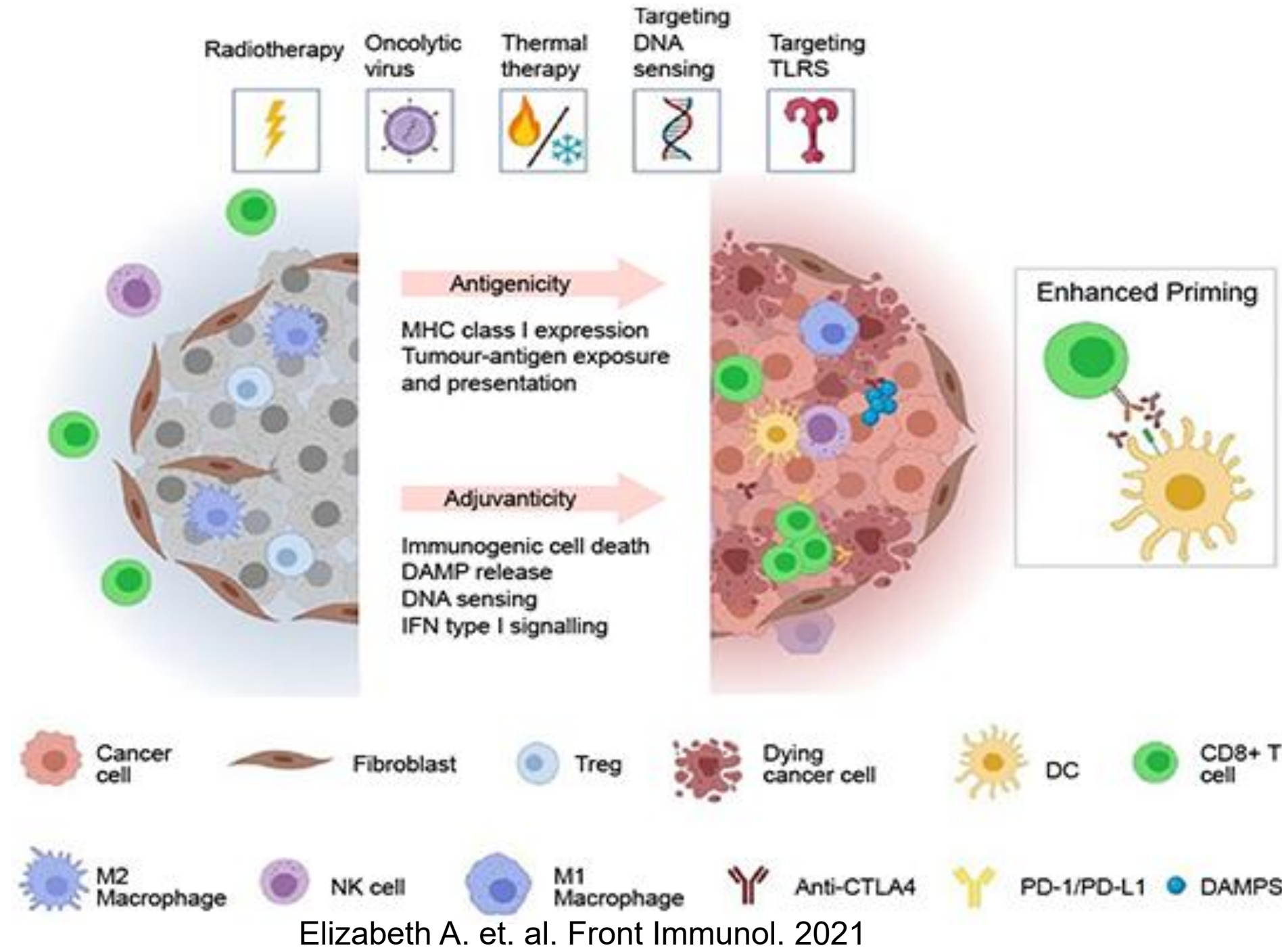
Targeting DNAPKCs to Overcome Immune Cold Phenotype and Immunotherapy Resistance in SCLC

Correspondence: triparna.sen@osumc.edu

INTRODUCTION

Small Cell Lung Cancer

- SCLC tumors are immunosuppressed with Low expression of PD-L1, epigenetic repression of MHC-I and decreased immune-cell infiltration
- Elevated expression of DDR protein to sustain high proliferative rate
- DNAPKCs orchestrates NHEJ DNA repair mechanism



Hypothesis: DNAPKCs inhibition will sensitize tumor cells, induce anti-tumor immune response, and enhance the anti-tumor effect of immune checkpoint blockade in SCLC.

METHODS

Design:

- Retrospective bioinformatic analysis of real-world patient samples.
- Cell viability analysis.
- Confocal microscopy-based immunofluorescence.
- Immunoblot and quantitative RT-PCR analysis.
- Immunocompetent GEMMs of SCLC.
- Flow cytometry.

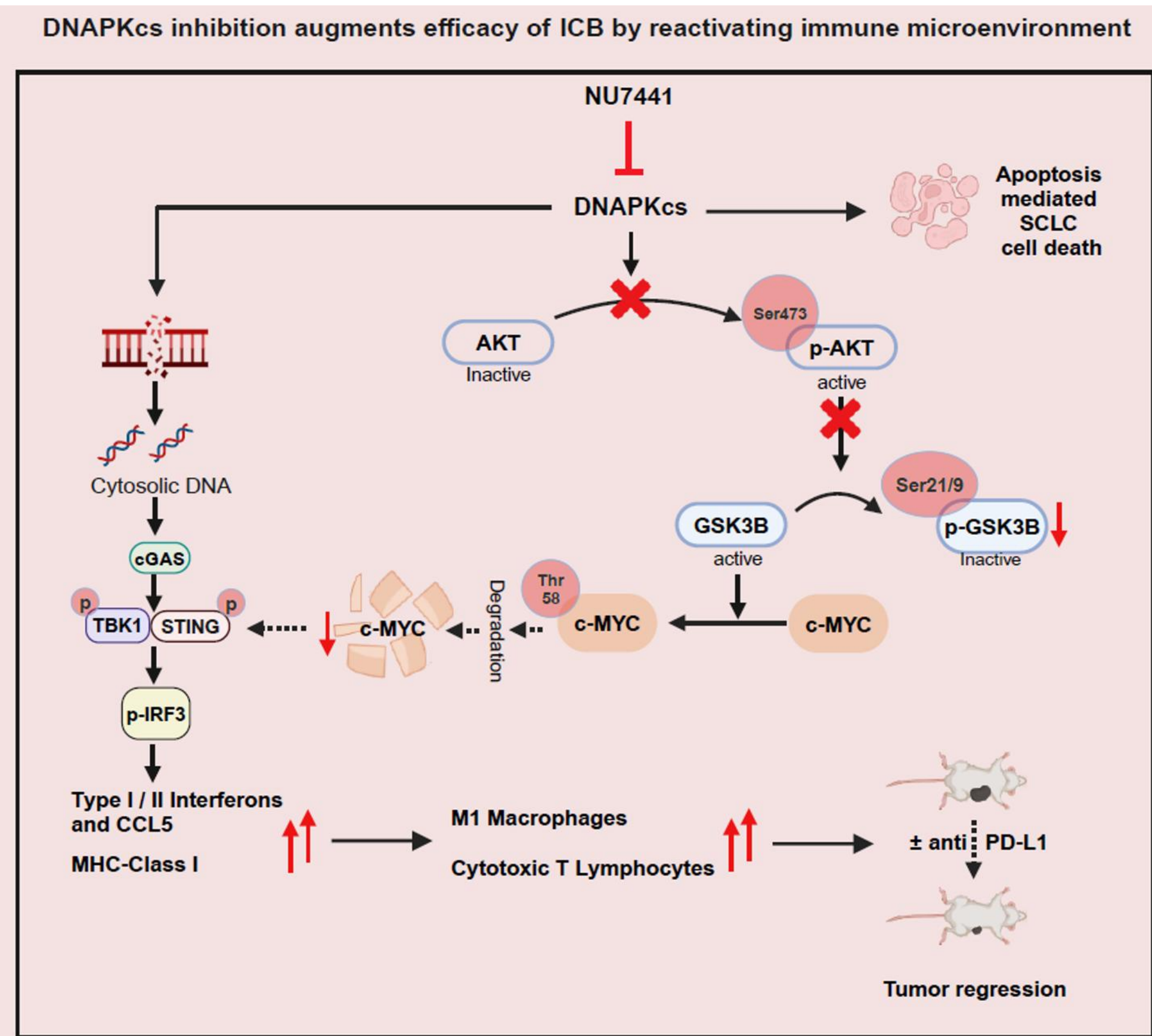
REFERENCES & ACKNOWLEDGEMENTS

- This work is supported by NIH/NCI R01 CA258784; Congressionally Directed Medical Research Programs (DOD-IITRA) LC190161.
- Chakraborty, S., Elliott, A., Sen, U. et al. Targeting NHEJ activates STING signaling through MYC degradation to boost antitumor immunity in SCLC. Nat Commun 17, 2597 (2026). <https://doi.org/10.1038/s41467-026-69262-x>

Use QR code to save space and to link to more extensive lists or related works.



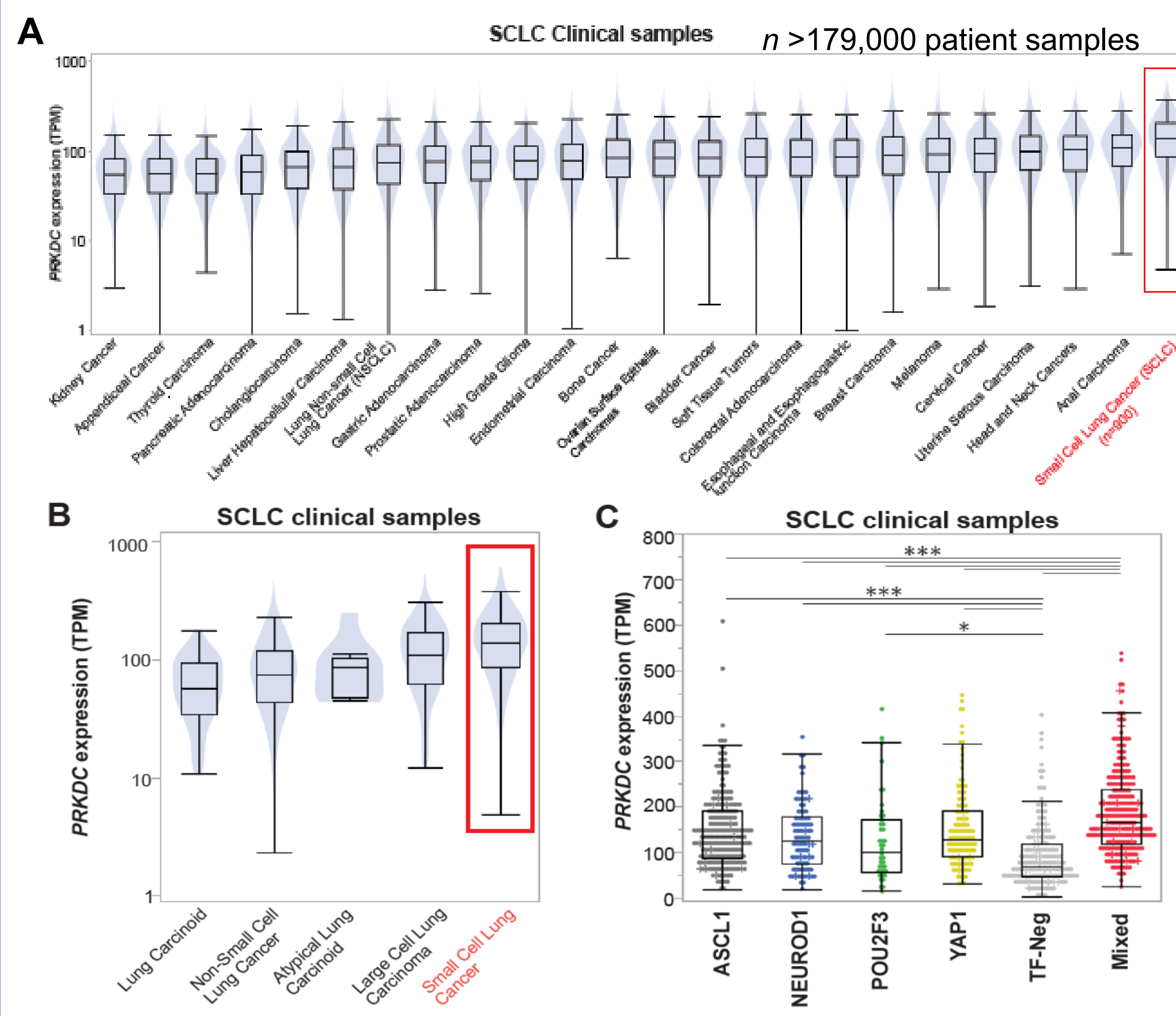
DISCUSSION AND CONCLUSION



- ❖ DNAPKCs represents a therapeutic vulnerability in SCLC.
- ❖ DNAPKCs Inhibition leads to DNA damage, destabilizes MYC, and activates cGAS–STING signaling.
- ❖ DNAPKCs inhibition synergized with PD-L1 blockade to drive STING-dependent durable tumor regression.
- ❖ DNAPKCs inhibition restore MHC-I expression, promote immune infiltration.

RESULTS

Figure 1: DNAPKCs in highly expressed in SCLC



RESULTS

Figure 2: High DNAPKCs expression in SCLC patients predicts worse prognosis

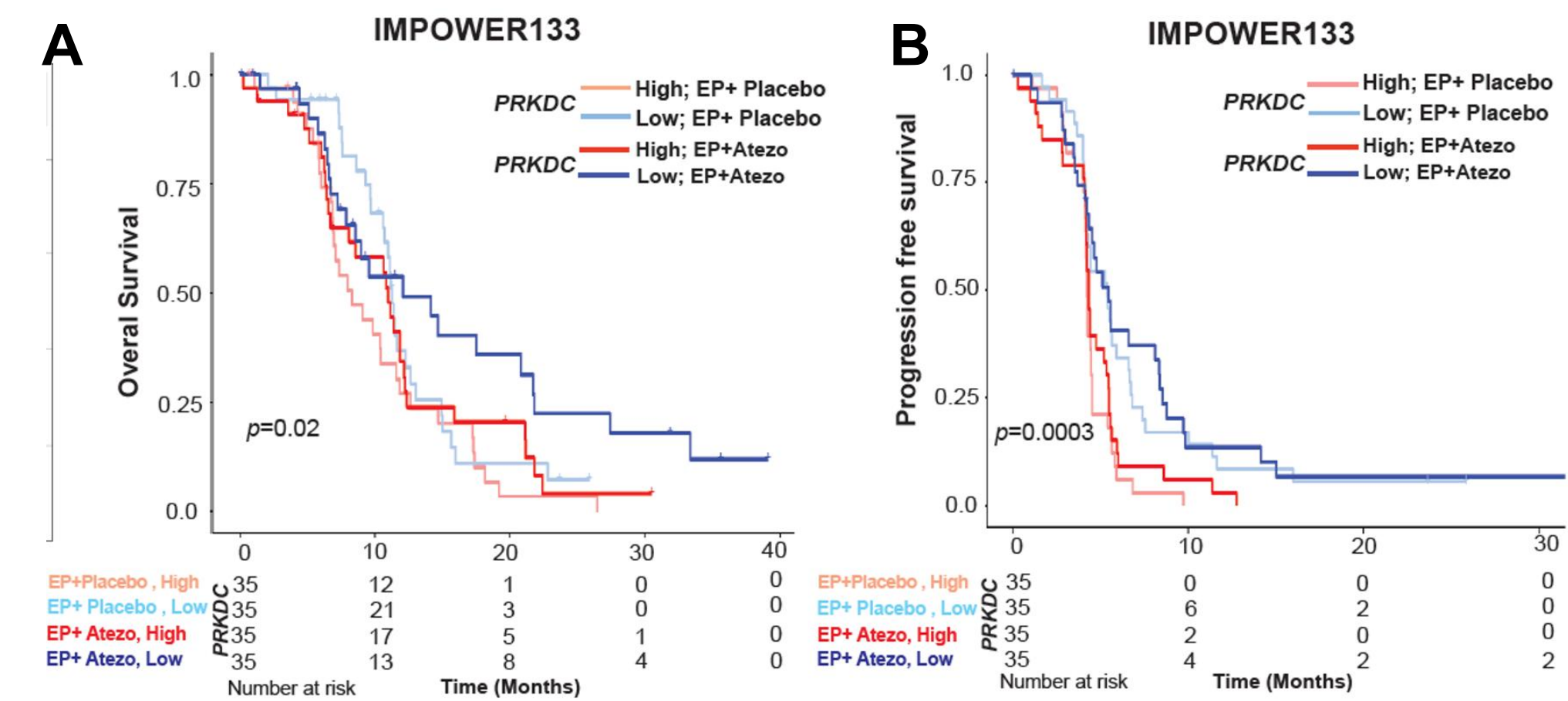


Figure 3: SCLC cells are sensitive to pharmacological inhibition of DNAPKCs

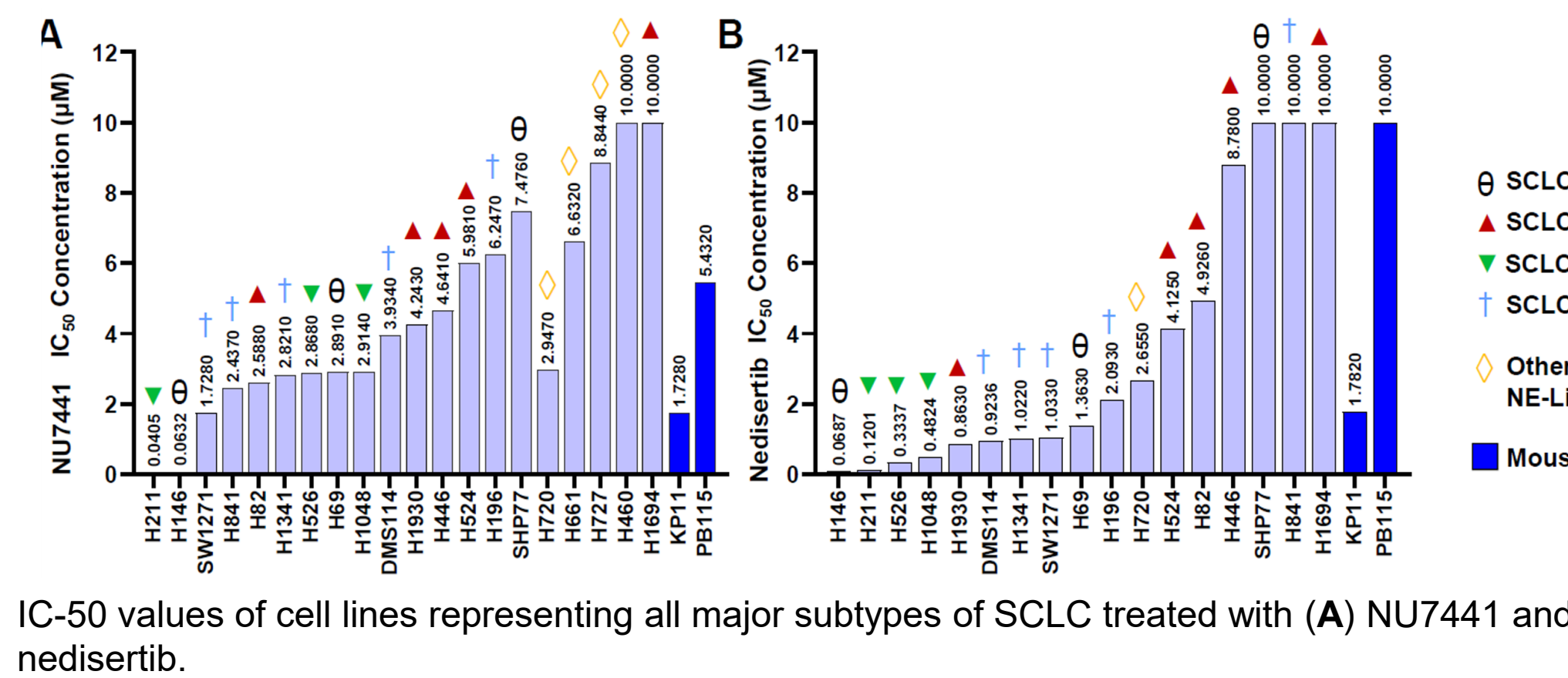


Figure 4: DNAPKCs inhibition facilitates formation of micronuclei to be recognized by cGAS

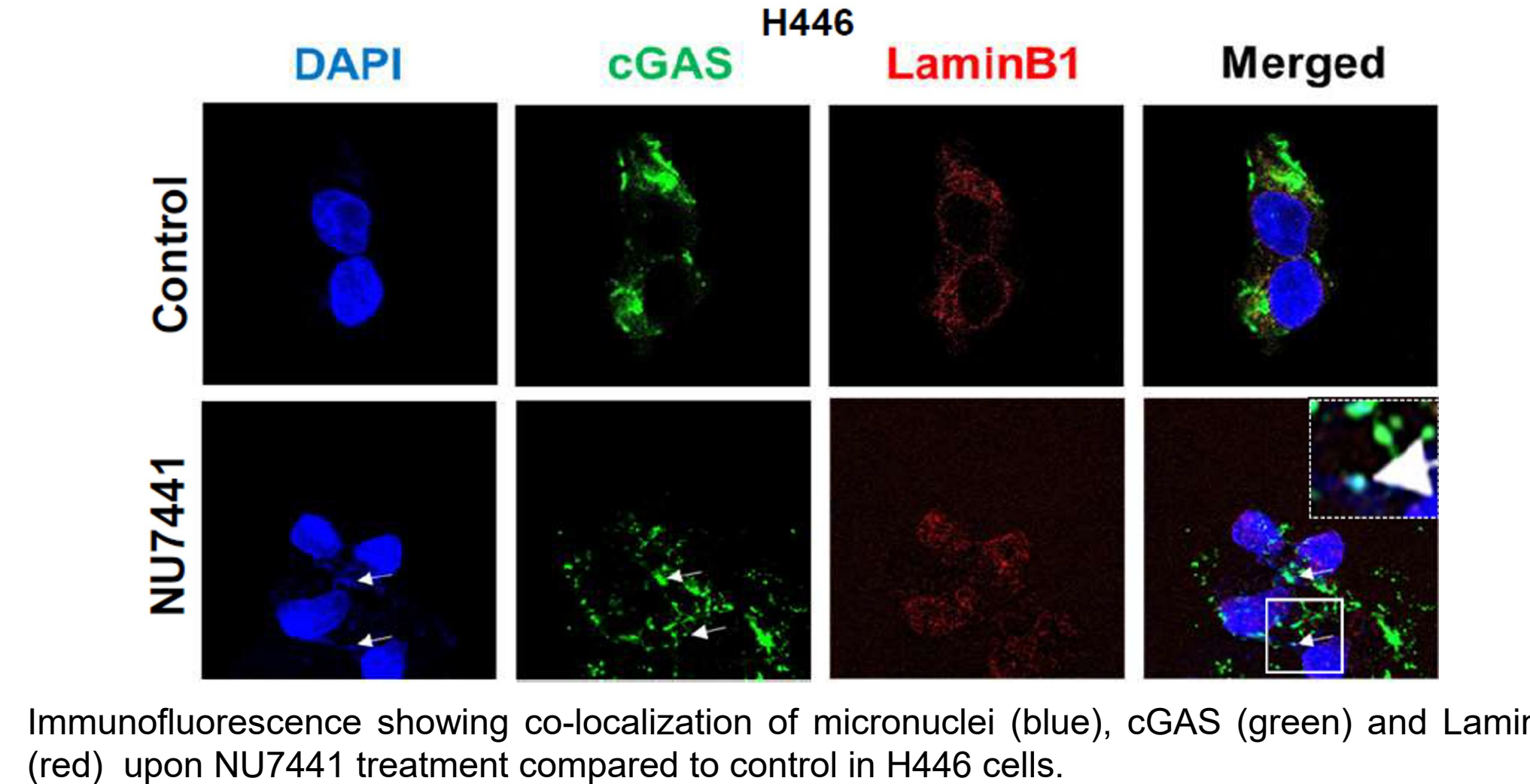


Figure 5: DNAPKCs inhibition activates cGAS-STING pathway and facilitates MYC degradation

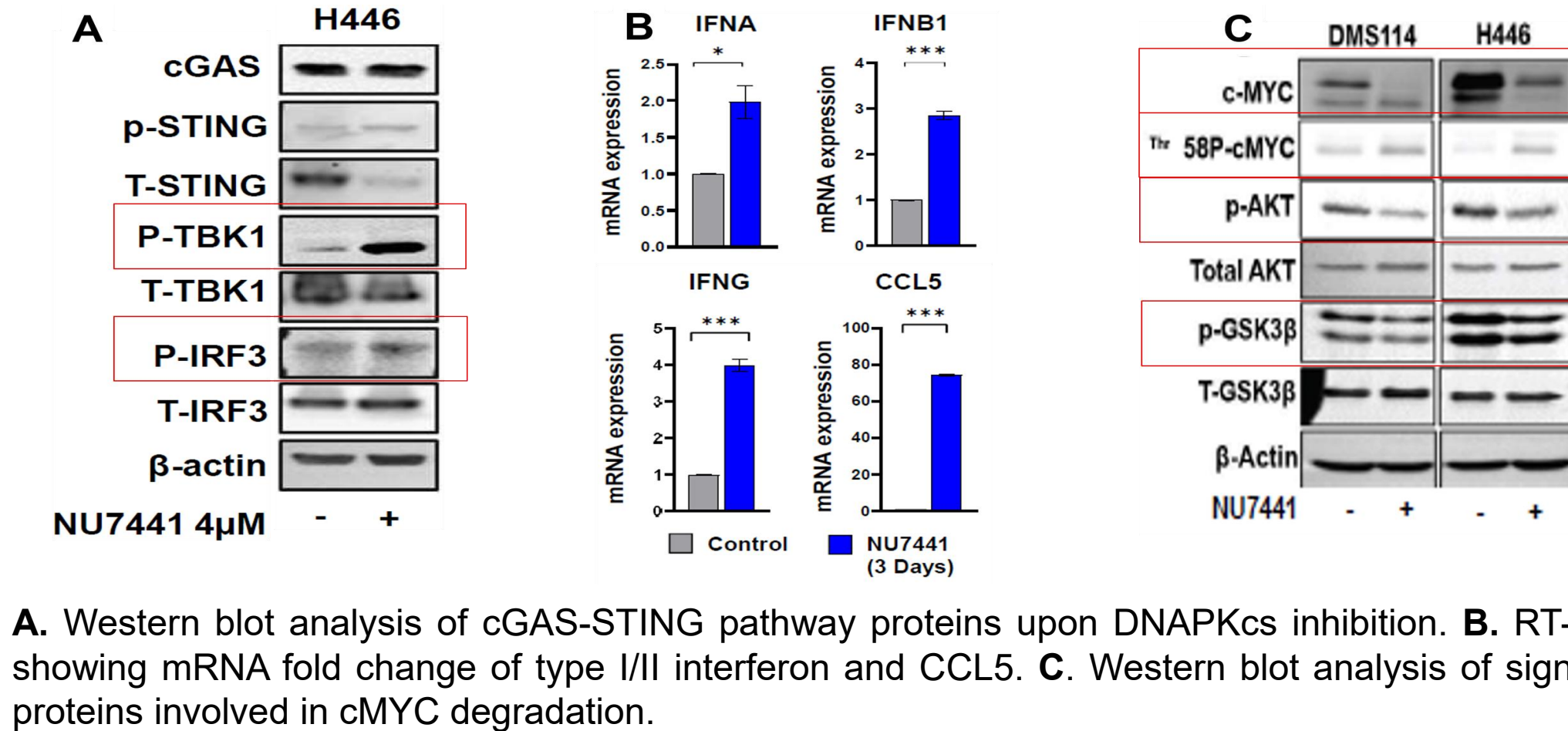


Figure 6: MYC overexpression reverses the immunogenic effects of DNA-PKCs inhibition

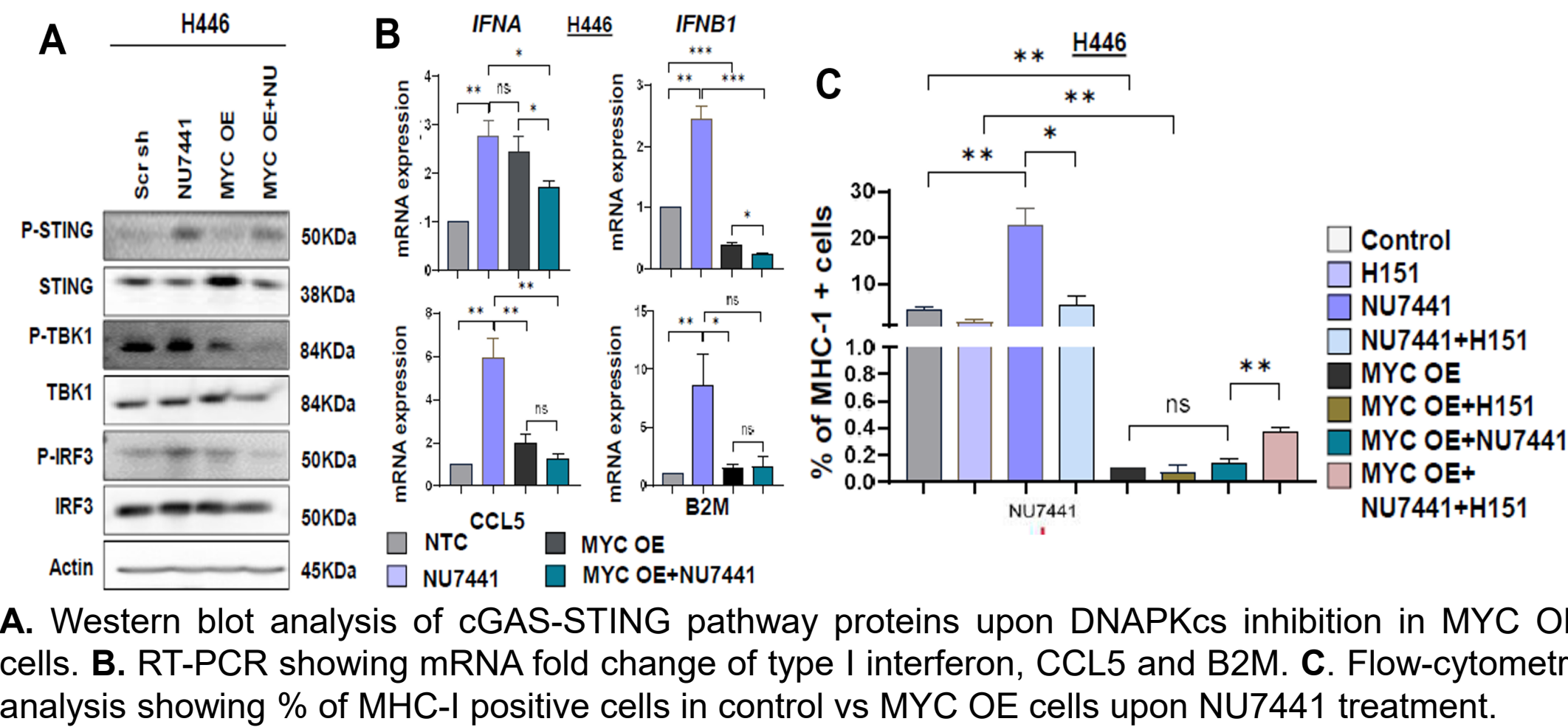


Figure 7: DNAPKCs inhibition ± anti-PD-L1 results in significant tumor regression in in-vivo GEM models of SCLC and modulates tumor immune microenvironment

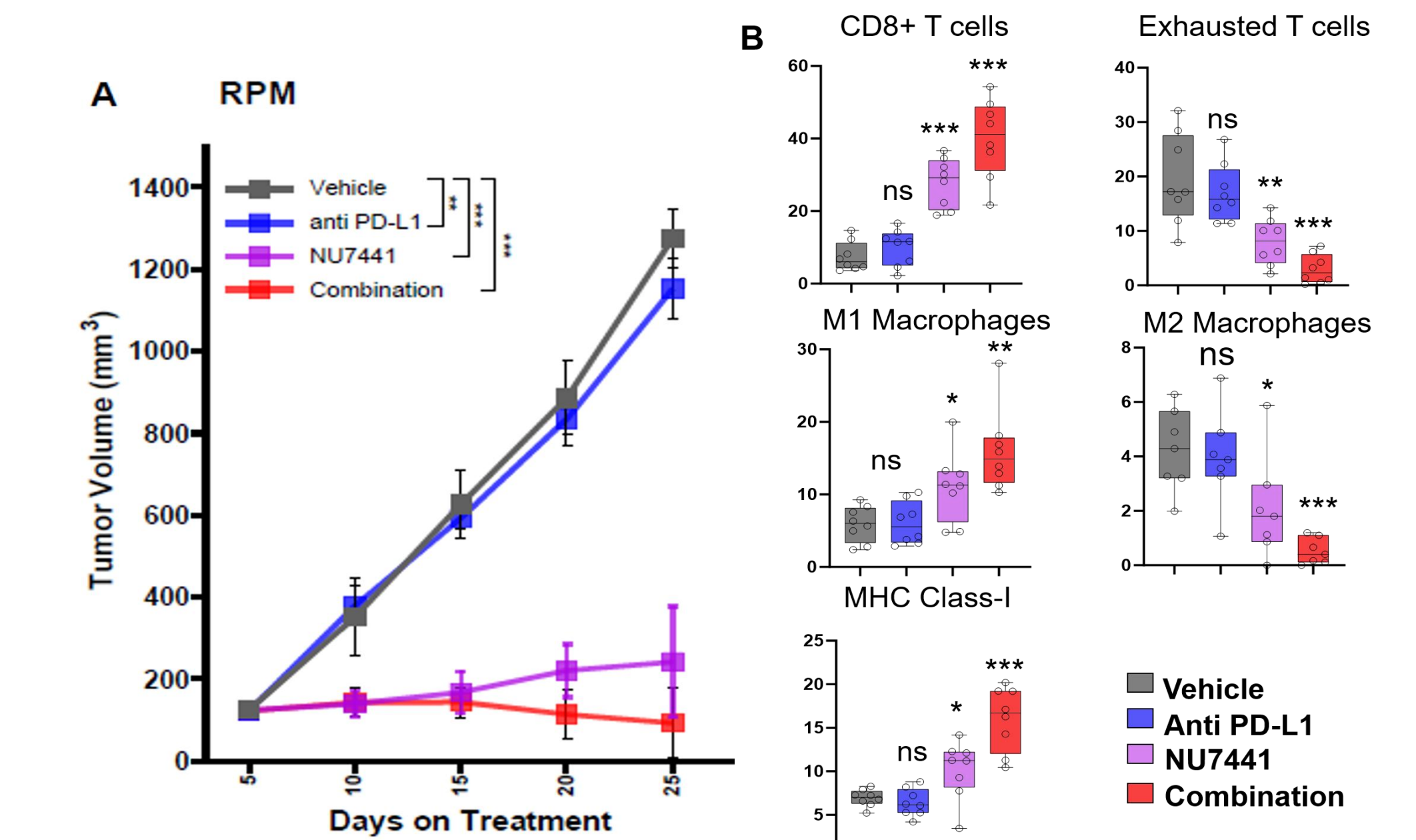


Figure 8: STING inhibition overcomes anti-tumor efficacy and immune response of DNAPKCs inhibition

