2020

# Combination Therapies of Guadecitabine and Immune Checkpoint Inhibitors in a Murine Triple-Negative Breast Cancer Model

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# Combination Therapies Including Guadecitabine in E0771 Murine Triple-Negative Breast Cancer Model

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## Background

- Cancer is the second leading cause of death in the U.S. Triple-negative breast cancer (TNBC) is associated with poor prognosis due to lack of estrogen receptor (ER-), progesterone receptor (PR-), and amplified human epidermal growth factor receptor 2 (HER2-), so other targets are needed.
- Dysregulation of the MEK pathway is a mechanism commonly involved in the proliferation and immune evasion of malignant cells, including TNBC. Trametinib is a MEK1/2 inhibitor that may inhibit tumor growth.
- One of the hallmarks of cancer is avoiding immune destruction. Various mechanisms used for immune evasion include upregulation of immune checkpoint molecules (like PD-1/L1), hypermethylation of tumor suppressors, induction of immune-suppressive cells, downregulation of MHC class I, and immunoediting. These mechanisms can be inhibited using a DNA methyl-transferase inhibitor (DMTi)
- Guadecitabine is a next-generation DMTi that is more stable and lasts longer in circulation than its parent molecule, decitabine. Guadecitabine has been found to augment anti-tumor T cell activity in adoptive immunotherapy (AIT) in other murine TNBC models.
- Recently, a regimen of Taxol (paclitaxel) and Atezolizumab (anti-PD-L1) was approved for clinical trials treating metastatic TNBC. Guadecitabine may improve the efficacy of this regimen.

## Acknowledgements

- Special thanks to Dr. Bear for hosting me in his lab and mentoring me for three semesters and to Laura Graham for training me and for assisting in data collection.
- Funded by Massey Cancer Center, Women & Wellness Funds
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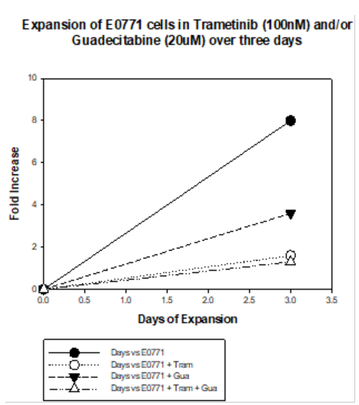
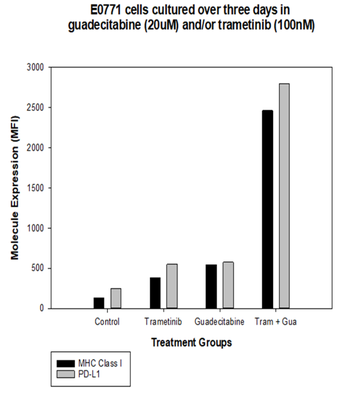
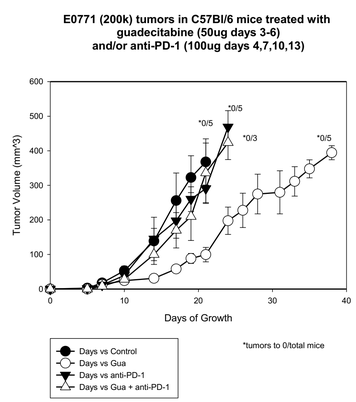
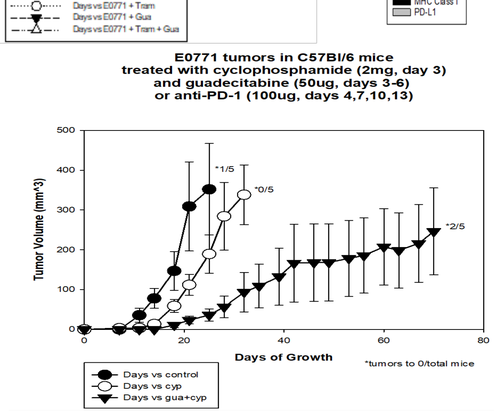
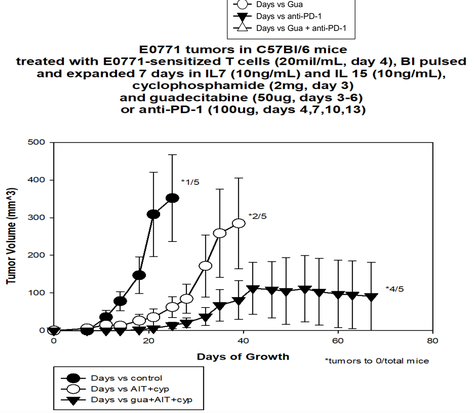
## Results

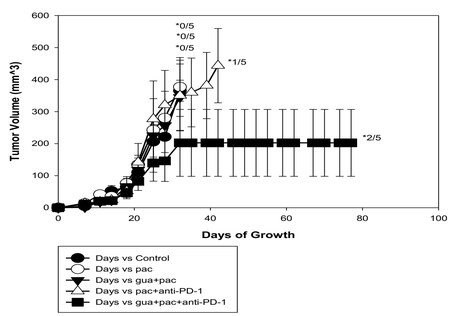


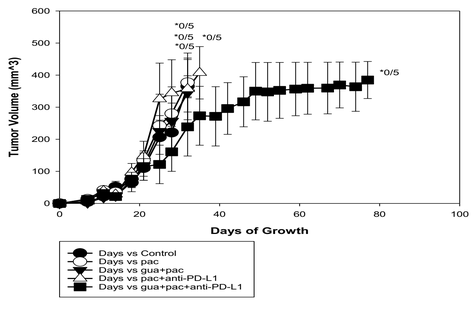




## Methods

- All mice were inoculated with 200 thousand E0771 cells suspended in PBS (1X) via subcutaneous injection to establish tumors on the left flank. Tumor volumes were measured twice per week (every 3 or 4 days) starting post-inoculation day 7 along two axes (length and width) and tumor volumes were calculated as (length/2)(width$^2$).
- E0771 cells were maintained in complete Roswell Park Memorial Institute (RPMI) cell medium plus 10% fetal bovine serum (FBS), 0.075% sodium bicarbonate, 1mM sodium pyruvate, 0.1mM non-essential amino acids (NMEM) (1X), 100 units/mL penicillin, 100µg/mL streptomycin, 10mM hepes, 5x10$^{-5}$ M 2-mercaptoethanol, and 2mM L-glutamine. The cells were harvested using 0.05% trypsin-EDTA.

## Conclusions

- Guadecitabine alone and in combination with trametinib increases PD-L1 and MHC class I expression and inhibits cell proliferation *in vitro*
- Early treatment with guadecitabine significantly suppresses initial tumor growth *in vivo*
- Guadecitabine combined with AIT is highly effective at suppressing tumor growth and produces a high cure rate
- Treatment with guadecitabine combined with paclitaxel and anti-PD-1/L1
- Paclitaxel may not be the best partner for guadecitabine.

## Future Directions

- Repeat studies in 4T1 murine TNBC model
- Studies of cell populations in solid tumor, tumor microenvironment, and lymphatic organs after treatment
- Guadecitabine, paclitaxel, and anti-PD-1/L1 with AIT
- Guadecitabine and Adriamycin and anti-PD-1/L1