

ENHANCEMENT OF ANTI-TUMOR EFFICACY OF IMMUNE CHECKPOINT BLOCKADE BY ALPHA-TOCOPHERYLOXACETIC ACID-LYSINE

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Background While much success has been achieved with immune checkpoint blockade (ICB)-targeted therapies, curative responses occur in only a fraction of patients. Adjuvant chemotherapy, which frequently consists of DNA targeting agents, while necessary, can contribute to additional acute toxicity and side effects to the immune-related toxicities inherent in the use of immune checkpoint. These limitations can negatively impact the quality of life of patients during and after treatment and highlight the need for safer, less toxic anti-cancer agents that can be used in combination with ICB to improve patient outcomes. Alpha-Tocopheryloxy acetic acid-Lysine (a-TEA-LS) is a scalable salt form of alpha-TEA that exhibits tumor cytotoxicity by preferentially targeting dysregulated tumor cell mitochondria to generate toxic reactive oxygen species that trigger immunogenic cell death (ICD). This activity causes release of "danger signals" including heat shock proteins, ATP, Calreticulin and HMGB-1 and generates antigen-containing autophagosomes which stimulate cross-presentation within dendritic cells leading to antigen-specific T cell priming. **Methods** Mice bearing established 4T1 mammary tumors were treated with alpha-TEA-lysine salt in combination with the immune checkpoint blockade antibodies anti-PD-1, anti-PD-L1, and anti-CTLA4 and monitored for tumor growth suppression, and overall survival. The combination treatment group that was not effective in controlling 4T1 tumor growth was evaluated for anti-tumor activity against MMTV-PyMT and Eph4 1424 mammary tumors.

Results Combination therapy consisting of alpha-TEA-Lys+anti-PD-1 or alpha-TEA-Lys+anti-CTLA4 but not of alpha-TEA-LS +anti-PD-L1 controlled tumor growth in the 4T1 tumor model. Anti-PD-L1 which had no impact on growth of 4T1 tumors inhibited tumor growth and increased overall survival in MMTV-PyMT and Eph4 1424 tumor models. When compared with an immunogenic cell death inducing agent, Doxorubicin, a-TEA-LS+anti-PD-L1 treatment, both treatments were effective in controlling tumor growth but the alpha-TEA-LS +anti-PD-L1 treatment was better tolerated than Doxorubicin +anti-PD-L1 treatment. Mice on the alpha-TEA/anti-PD-L1 therapy demonstrated no weight loss whereas mice in the Doxorubicin/anti-PD-L1 treatment group demonstrated ruffling, were hunched and experienced significant weight loss.

Conclusions The data demonstrate that the efficacy of ICB therapy is dependent on the mammary tumor model and on the type of ICB antibody used. Based on the safety profile of a-TEA-LS and the enhanced anti-tumor efficacy demonstrated by a-TEA-LS+ICB in these pre-clinical mammary tumor models, a-TEA-LS has the potential to be used as an adjuvant therapeutic to improve the effectiveness of ICB in human breast cancer. Experiments are underway to interrogate the immune tumor microenvironment to find out what role they may play in the different responses observed.

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