INTRODUCTION

High levels of extracellular adenosine generated in the tumor microenvironment (TME) engage A2a and A2b adenosine receptors on immune cells, resulting in immunosuppression (Figure 1). Chemotherapy releases adenosine triphosphate (ATP) into the tumor microenvironment, where it is rapidly converted into adenosine, primarily by the ectonucleotidases CD39 and CD73. Etrumadenant (etruma) is a selective, small molecule, dual A2a/A2bR antagonist, which was specifically designed to potently block adenosine-induced immunosuppression in the TME. We previously showed that etrumadenant blocks the immunosuppressive effects of adenosine in immune cells and enhances anti-tumor immune responses in mouse syngeneic tumors. Herein, we describe the capacity for etruma to drive enhanced tumor control and immune activity in mouse tumor models using immunotherapeutic chemotherapeutic agents with different chemotherapy doses or with different dosing regimens.

Etrumaden is currently being studied in several preclinical studies in combination with chemotherapy or other immune-enhancing regimens: NCT04383832, NCT04680012, NCT04823856.

METHODS

Imbied intact cell experiments: C57B1 T cells and dendritic cells (DC) were isolated from healthy human blood by negative selection. DC were matured with LPS/IFN-γ for 24 hours in the presence of NECA (synthetic adenosine receptor agonist) or A2B agonist.

CRE phosphorylation assay: C6 cells, which express A2aR, were stimulated with 10 ng/ml IL-2 or 50 ng/ml ATP, and CRE phosphorylation was measured by Western Blot and densitometry.

Etrumaden is Highly Expressed on Cancer Cell - R/A (Figure 2A) and Drives Gene Expression Changes Which Are Blocked by Etrumaden (Figure 2B - 2F).

RESULTS

Adenosine Signaling Drives Suppression Through A2aR and A2bR in Immune Cells Which Is Reversed by Etrumaden

Etrumaden Inhibits Peripheral CREB Phosphorylation and Suppresses B16F10 Tumor Growth

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Etrumaden Combines with Platinum-Based Chemotherapy to Enhance AT3-OVA Tumor Control and Immune Infiltration

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Etrumaden Combines with Doxorubicin Chemotherapy to Enhance AT3-OVA Tumor Control and Immune Infiltration

CONCLUSIONS

These studies demonstrate the ability of etrumaden to block adenosine-driven immunosuppression and to combine with chemotherapeutic agents in preclinical models.

Furthermore, our studies suggest that combination of etrumaden with a trumped course of immunomodulatory (either fewer cycles or a reduced dose level) may be sufficient to achieve tumor arrest and yield similar anti-tumor effects as a full course of chemotherapy.