THE ANTI-TUMOR EFFICACY OF IMMUNOGENIC CHEMOTHERAPY IS ENHANCED BY THE DUAL $A_{2A}$R/$A_{2B}$R ANTAGONIST ETRUMADENANT, RELIEVING THE NECESSITY FOR AN EXTENDED CHEMOTHERAPY REGIMEN

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Background Generation of extracellular adenosine is a hallmark of cancerous tissue and drives immunosuppression that facilitates tumor growth/survival. Chemotherapy releases adenosine triphosphate into the tumor microenvironment, where it is rapidly converted into adenosine, primarily by the ectoenzymes CD39 and CD73. Recent studies have demonstrated that certain chemotherapies can enhance the expression of tumoral CD73, suggesting that inhibition of adenosine generation and/or signaling might enhance the immune-activating and anti-tumor effects of those chemotherapeutic agents. Indeed, our preclinical studies with the dual $A_{2A}$R/$A_{2B}$R antagonist etrumadenant (etruma) have shown a marked ability to suppress mouse syngeneic tumor growth and enhance intratumoral T cell infiltration when combined with immunogenic chemotherapies. Various etruma/chemotherapy combinations are currently being studied in clinical trials. We have investigated the capacity of etruma to drive enhanced tumor control and immune activation in mouse tumor models, in combination with lower chemotherapy doses or reduced dosing regimens.

Methods Mice were inoculated with either AT3-OVA or 4T1 syngeneic cancer cell lines. Mice with established tumors were dosed with oxaliplatin or doxorubicin, alone or in combination with etruma and the effects of the various treatments on tumor growth were assessed. Tumors were removed for histologic analysis or analysis of immune cell infiltration by flow cytometry.

Results Etruma increased anti-tumoral activity and tumor infiltration of antigen-specific CD8+ T cells across a dose range of oxaliplatin using the AT3-OVA mammary cancer model. Similar results were also found using the 4T1 model, a strongly CD73+ tumor, in which a combination of etruma with doxorubicin showed a reduction in both primary tumor growth and metastatic tumor burden. Following these results, we investigated whether a shorter course of chemotherapy could provide similar therapeutic benefit in combination with etruma. Using the AT3-OVA model, etruma significantly enhanced the efficacy of doxorubicin at both low and higher doses (3 vs 5 mg/kg). Interestingly, a shorter course of doxorubicin (2 doses) in combination with etruma provided similar efficacy and was statistically indistinguishable from the full course of chemotherapy (4 doses), indicating that the greatest therapeutic benefit of chemotherapy, when combined with etruma, may result from the initial, priming, doses of chemotherapy.

Conclusions These findings demonstrate a clear benefit for etruma combinations with chemotherapeutic agents in preclinical models. Furthermore, our most recent studies suggest that a truncated course of immunogenic chemotherapy plus etruma may be sufficient to enhance immune activation and yield similar anti-tumor effects as a full course of chemotherapy.