COMBINATION OF ADENOSINE ANTAGONISTS A2AR (TT-10) AND A2BR (TT-4) WITH CHECKPOINT INHIBITORS DEMONSTRATE ANTI-TUMOR ACTIVITY IN CT-26 MURINE COLON TUMOR ALLOGRAFT MODEL

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Background TT-10 and TT-4 are potent and selective antagonists of adenosine A2A receptor (A2AR) and A2B receptor (A2BR) respectively. Both agents are being developed for the treatment of advanced cancers initially as monotherapy, using high levels of adenosine receptor expression in tumor tissue as biomarker.

Methods Balb/c mice were implanted with CT-26 cells and randomly assigned to 8 groups per study; (1) vehicle control, (2) adenosine antagonist - 1 mg/kg A2AR (TT-10) 1 mg/kg or 3 mg/kg A2BR (TT-4), (3) 10 mg/kg Anti-mPD-1, (4) 5 mg/kg Anti-mCTLA-4, (5) 100 mg/kg Irinotecan, (6) adenosine antagonist + Anti-mPD-1, (7) adenosine antagonist + Anti-mCTLA-4, (8) adenosine antagonist+ Irinotecan. Adenosine antagonists and control were given daily by oral gavage, Anti-mPD-1, Anti-mCTLA-4 and Irinotecan were administered Intraperitoneal. Treatment was started on day 1 post implant and mice were followed until individual tumor volume reached 2,000 or 3000 mm³ (as defined by protocol) or moribund. Tumor measurements and weights were taken every 2 to 3 days. In addition, a subset of mice were investigated for changes in peripheral whole blood and intra-tumor analysis on days 3 and 10 via flow cytometry. The populations of interest included CD223+, CD3+, CD4+, CD8+, CD25+FoxP3+, CD25-CD69+ and CD44+CD62L.

Results All implanted mice developed measurable tumors. Mean suppression of tumor growth was observed to be greater in single agent adenosine antagonists TT-10 and TT-4 when compared to the vehicle control and was observed to show overall greater suppression of tumor growth when combined with anti-mPD-1 or anti-m-CTLA-4. Tumor infiltrating lymphocyte analysis by flow cytometry, showed higher amounts of CD25+FoxP3+ present in control mice at day 3, than was observed in mice that were treated with A2AR alone, A2AR + anti-mPD-1 and A2AR + anti-m-CTLA-4.

Conclusions TT-10 and TT-4 alone was superior to vehicle control in slowing tumor growth. However, the combination of TT-10 + Anti-mPD-1 and TT-4 + Anti-mCTLA-4 showed the greatest tumor response and growth suppression. Furthermore, a striking reduction of CD25+FoxP3+ within the tumor was observed at day 3 in mice treated with A2AR alone, A2AR + anti-mPD-1 and A2AR + anti-m-CTLA-4 when compared to the vehicle control.

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