A novel non-competitive and non-brain penetrant adenosine A2A receptor antagonist designed to reverse adenosine-mediated suppression of anti-tumor immunity

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SUMMARY
• High levels of extracellular adenosine drive tumor immunosuppression
• Adenosine concentrations in tumors are at least 10-fold higher compared to normal tissue
• A2A is the most prevalent adenosine receptor of immune cells
• Adenosine suppresses innate and adaptive immune reactions via signaling through A2A
• A2A antagonists repurposed from Parkinson’s disease dramatically loose potency in a high adenosine environment
• iTeos A2A antagonist is designed for immuno-oncology:
  ✓ Non-competitive and selective inhibitor of A2A
  ✓ Highly potent in high intratumoral adenosine concentrations
  ✓ Non-brain penetrant, avoiding potential CNS side-effects at doses needed to inhibit tumoral A2A
  ✓ Rescues adenosine-driven T cell and innate cell immunosuppression
  ✓ Increases in vivo anti-tumor efficacy of a-CTLA4 and a PD1

HIGH EXTRACELLULAR ADENOSINE CONCENTRATION IN TUMORS
Adenosine concentrations in patient-derived xenografts. Extracellular adenosine content was measured in 10 PDX from the indicated tumor histological types and normal tissue. Extracellular fluid from the PDX was obtained by microdissection and adenosine was quantified by LC-MS. The mean adenosine concentration was 10.71 ± 1.70 µM (SEM) (n = 5 to 6 tumors/PDX model).

ADENOSINE-DRIVEN IMMUNOSUPPRESSION

ITEOS A2A ANTAGONIST IS POTENT, SELECTIVE AND NON-BRAIN PENETRANT

ITEOS A2A ANTAGONIST IS HIGHLY POTENT IN THE ADENOSINE RICH TUMOR MICROENVIRONMENT

ITEOS A2A ANTAGONIST IS A NON-COMPETITIVE INHIBITOR OF A2A

ITEOS A2A ANTAGONIST INCREASES T CELL CYTOTOXICITY

ITEOS A2A ANTAGONIST INCREASES ANTI-TUMOR EFFICACY OF CHECKPOINT INHIBITORS

CONCLUSIONS
iTeos A2A antagonist is a novel, best-in-class A2A antagonist designed for Immuno-Oncology:
• Non-competitive with adenosine
• Potent in high intratumoral adenosine concentration
• No CNS penetrance
• Reverses adenosine-mediated suppression of cancer immunity, including in high adenosine concentrations found in most human cancers