The Unmet Medical Need

Checkpoint inhibitors have quickly become a cornerstone in the treatment of numerous cancers, but are only effective for 20–30% of eligible patients. Patients with certain cancers, such as non-small cell lung cancer (140K patients), prostate cancer (75K patients), and colorectal cancer (85K patients), have limited options beyond chemotherapy and some targeted therapies if they are resistant to first-generation checkpoint inhibitors.

Target Rationale: ADORA2A for Immuno-Oncology

High concentrations of adenosine are generated through tumor-induced tissue disruption, hypoxia, and inflammation. Through activation of ADORA2A, the primary adenosine receptor on immune cells, adenosine creates an immunosuppressive microenvironment where tumors can evade immune responses. Inhibition of ADORA2A helps block immunosuppression, making it an attractive target to combat a broad range of cancers. ADORA2A antagonists have also been shown to synergize with standard-of-care immuno-oncology agents, such as anti-PD1, in combination therapies.

An antagonistic therapeutic antibody targeting ADORA2A has the potential to offer high potency, high specificity, and low CNS permeability.

Twist’s ADORA2A Antagonist Antibodies: TB206-001 and TB206-007

Twist has discovered two fully human IgG1 antibodies, TB206-001 and TB206-007, that bind specifically and with high affinity to ADORA2A. The antibodies behave as functional antagonists with IC50s in the single-digit nanomolar range (TB206-001 = 5.9 nM; TB206-007 = 1.7 nM) and reduce tumor growth in an in vivo mouse model of human colon cancer (Figure 1). This potent activity and enhanced potential for developability make TB206-001 and TB206-007 unique and encouraging pre-clinical antibodies against a promising next-generation immuno-oncology target*.

Additional Advantages

- Potential to be first-in-class antibody antagonist of ADORA2A
- Potent in vitro activity in a primary T-cell assay
- Inhibits tumor growth in a mouse model for human colon cancer
- Reduced potential for downstream manufacturing liabilities

Figure 1. Representative TB206-007 inhibits tumor growth in an in vivo mouse model for human colon carcinoma.