**CHECKPOINT INHIBITION AND THE TIGIT PATHWAY**

- The programmed cell death protein-1 (PD-1) inhibitory pathway is a key immune checkpoint that can be exploited by tumors to enable their survival.
- Zimbelimab (AB154), a monoclonal antibody (mAbs) in early clinical development, potently blocks PD-1 and has an anticipated safety profile similar to other approved anti-PD-1 mAbs.
- The T cell immunoreceptor with and ITIM domain (TIGIT) inhibitory pathway has been previously identified as a novel immune checkpoint that influences the antitumor immune response. 
- TIGIT, expressed on T cells and NK cells, binds tumor cell-expressed ligand CD155 and as a result, immune cell effecter function is abrogated.
- CD155 has a greater affinity for TIGIT, but can also bind the receptor DNAJ accessory molecule-1 (DNAJ1). If this occurs, the resulting signaling leads to increased tumor cell survival and tumor growth.

**RATIONAL FOR TIGIT COMBINATIONS IN NSCLC**

- For locally advanced or metastatic NSCLC, first-line treatment has historically included platinum-containing chemotherapy. Median overall survival and 5-year survival rates associated with these regimens are low.
- Immunotherapy agents, including PD-1/A2aR, have improved outcomes for patients with NSCLC. However, many patients neither initially respond to checkpoint inhibitors nor have durable responses, leaving an unmet need for new therapeutic approaches.
- Combinatorial therapy that blocks inhibitors of the adenosine, TIGIT, and/or PD-1 pathways may hold promise for increasing efficacy without introducing significant toxicity or potential synergistic antitumor activity.
- In preclinical studies, blocking TIGIT in combination with PD-1 treatment yields greater antitumor activity and survival relative to either agent alone.
- In patients with NSCLC, the adenosine pathway is a potential mechanism of resistance to anti-PD-1/anti-TIGIT1-4 and high tumor expression of CD39 is associated with poor prognosis11, which may indicate a therapeutic advantage to combination A2aR/PD-1 and PD-1 blockade.

**TUMOR IMMUNOLOGY**

- Tumors from patients with NSCLC have high expression of TIGIT, DNAJ-1, and PD-1, suggesting that the TIGIT and PD-1 pathways may be particularly important for the growth and persistence of this tumor type (Figure 3).

**THE ADENOSINE AXIS IN CANCER**

- Dismantling the A2aR/A2bR (adenosine receptors 2a/2b) axis by A2aR blockade and/or adenosine depletion yields greater antitumor activity and survival relative to either agent alone.
- By binding adenosine receptors 2a and 2b (A2aR and A2bR) expressed on immune cells, adenosine promotes immunosuppression by inhibiting critical components of the antitumor immune response and ultimately enables tumor cells to evade destruction.

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