ZEN-3694 is an orally bioavailable, potent inhibitor of both bromodomains of the Bromodomain and Extra-Terminal domain (BET) family of proteins (BRD2, BRD3, BRD4, BRD5, and BRD7) that bind via their tandem bromodomains (BD1 & BD2) to acetylated lysines in histones and promote gene transcription. Tumor type-specific super-enhancer associations with key oncogenes involved in tumor pathogenesis have been identified in hematologic and solid tumor malignancies10. Inhibition of BET proteins results in their displacement from super-enhancers leading to down regulation of key oncogenic programs involving members of the MYC and BCL-2 families10. Additionally, BET inhibitors (BD2) target pathway involved in metastasis, such as the NF-κB and Wnt/β-catenin pathways10. BET inhibitors have been demonstrated as potential antigens and suppress tumor cellularity in numerous solid and hematologic malignancies.

Although PD1 antibodies have shown remarkable and durable efficacy in a portion of cancers, a variety of immune mechanisms contribute to both innate and acquired resistance in the majority of patients. These include upregulation of alternate tumor and T cell checkpoint receptors, recruitment of suppressive cells which dampen the T cell responses, and tumor mechanisms to decrease immune recognition. Here we show that BET inhibitors have an additional unique mechanism of action: they inhibit multiple complementary mechanisms of tumor immune escape, which suggest that they could synergize with immunotherapies.

Results

ZEN-3694 targets a unique set of checkpoint receptors, cytokines, and tumor factors

ZEN-3694 induces expression of the immune checkpoint receptor PD-L1 in a Phase I/II clinical trial

ZEN-3694 targets multiple suppressive factors, and influences T cell activation in MC-38 colon cancer syngeneic mouse models

ZEN-3694 is antagonistic with anti-PD1 in the MC-38 syngeneic mouse model

ZEN-3694 has the potential to increase the anti-tumor immune response

References


