ST101, a peptide antagonist of novel I/O target CEBPβ, reprograms MDSC polarization and promotes an immunomodulatory tumor microenvironment

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Introduction & Abstract

ST101, a first-in-class antagonist of CEBPβ, is currently being evaluated in the Phase 2 portion of an ongoing Phase 1-2 clinical study in patients with advanced unselected and metastatic solid tumors (NCT04547297). ST101 is an open-label, Phase 1-2 dose-finding study designed to determine the safety, tolerability, PK, PD, and proof-of-concept efficacy of ST101 in patients with advanced solid tumors. ST101 has demonstrated clinical proof-of-concept with a confirmed partial response in a patient with recurrent GBM, a durable RECIST 1.1 confirmed partial response (PR) in a patient with cutaneous melanoma and evidence of long-term stable disease in several additional patients.

COAT1/Enhancer Binding Protein β (CEBPβ) is a basic leucine zipper (bZIP) transcription factor that causes aberrant gene expression in many cancers. Upregulated or overexpressed CEBPβ drives oncogenesis by promoting tumor survival and proliferation and is critical of the immunosuppressive tumor microenvironment (TME). Specifically, CEBPβ regulates macrophage differentiation, activating a transcriptional program driving macrophage polarization toward immunosuppressive M2-type myeloid-derived suppressor cells (MDSCs). Consistently, activation of CEBPβ correlates with poor prognosis in several types of human cancer. Thus, targeting CEBPβ for reprogramming tumor-associated macrophages (TAMs) from the M2 toward the immune-promoting M1 phenotype represents an attractive strategy to enhance antitumor immunity. ST101 is a novel peptide antagonist of CEBPβ immunodominance that retains CEBPβ-independent gene expression. Here we evaluated the efficacy of ST101 on immune function in the murine mammary tumor model.

Peripheral Blood Mononuclear Cells (PBMCs) were activated toward the M1 or M2 phenotype by LPS and IFNγ or IL-4, respectively. ST101 and vehicle were added at concentrations of 10-8, 10-6, and 10-4 MCD1, C2D8, while inducing M1 markers (CD86, C68) by flow cytometry and quantitative PCR, resulting in an 40-60% increase in the M1M2 ratio without substantial impact on cell viability. Next, in cultures of T cells with MDSC macrophage, ST101 exposure resulted in a 50% increase in T-cell activation compared to control MDSC co-cultures, as measured by intracellular IFNγ staining. Importantly, ST101 did not suppress proliferation or activity of T cells cultured alone. Finally, in an orthotopic TNBC model in vivo, ST101 in combination with anti-PD1 treatment enhanced antitumor activity compared to either single agent alone. The observed increase in tumor growth inhibition was accompanied by a reduced tumor burden and improved overall survival compared to the untreated mice. ST101 is being evaluated in a Phase 1-2 clinical study in patients with advanced unselected and metastatic solid tumors (NCT04196279). In situ gene expression analysis performed in 9 paired patient samples showed that mice treated with ST101 and vehicle (n=9) at the different time points before or after ST101 administration during cycle 2 of therapy showed distinct dose escalation (4 mg/kg ST101 or greater) indicates a significant reduction in expression of immune checkpoint molecules involved in M2 polarization, including C2D8, S100Gl, and T-cell exhaustion markers. ST101 is a novel peptide antagonist of CEBPβ immunodominance that retains CEBPβ-independent gene expression. Here we evaluated the efficacy of ST101 on immune function in the murine mammary tumor model. ST101 is a novel peptide antagonist of CEBPβ immunodominance that retains CEBPβ-independent gene expression. Here we evaluated the efficacy of ST101 on immune function in the murine mammary tumor model. ST101 is a novel peptide antagonist of CEBPβ immunodominance that retains CEBPβ-independent gene expression. Here we evaluated the efficacy of ST101 on immune function in the murine mammary tumor model. ST101 is a novel peptide antagonist of CEBPβ immunodominance that retains CEBPβ-independent gene expression. Here we evaluated the efficacy of ST101 on immune function in the murine mammary tumor model.

Results

Figure 2. ST101 rescues M2-like macrophages in TNBC BM. A) Exemplary outline of TNBC M2-like macrophage populations identified using FACS. B) Flow Cytometry plot of the increased ST101 expression of CD68 positivity in TNBC conditions (ANOVA) compared to controls (n=163). C) Representative ST101 expression and intracellular IFNγ staining in BM cells from TNBC with highlighted populations of interest. (ANOVA) compared to controls (n=163). D) Flow cytometry plot of the increased ST101 expression of CD68 positivity in TNBC conditions (ANOVA) compared to controls (n=163). (A) A/B) ST101 rescues CD8 T cell T-cell activation in macrophage/T cell mixed cultures as measured by IFNγ production. (B) Sublethal ST101 enhances the activity of anti-PD1-T cell therapy in vivo in a murine mammary tumor model (M2) by reducing the total TAM and inducing a repolarization to the M1 identity in the TAM population. (C) ST101 modulates the tumor immune microenvironment in patient biopsies by suppressing genes required for M2 macrophage polarization, culminating in an enhanced CD8/Treg ratio. These data support a model in which ST101 promotes a shift in the tumor microenvironment by inhibiting the M2 program in unstimulated precursor macrophages in vitro and in vivo, resulting in reduction of TAMs and an increase in the M1RD ratio in vivo. and activation of cytotoxic T cells in a previously immunosuppressive environment.

Conclusions