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ST101, A PEPTIDE ANTAGONIST OF NOVEL I/O TARGET CEBP β , REPROGRAMS MDSC POLARIZATION AND DECREASES TUMOR-ASSOCIATED TREGS, SUGGESTING AN IMMUNE COMPONENT TO OBSERVED CLINICAL RESPONSES

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Background CCAAT/Enhancer Binding Protein β (C/EBP β) is a basic leucine zipper (bZIP) transcription factor that causes aberrant gene activation in many cancers. Upregulated or over-activated C/EBP β drives oncogenesis by promoting tumor survival and proliferation¹ and is a critical regulator of the immunosuppressive environment.² Specifically, C/EBP β regulates macrophage differentiation, promoting the expression of M2 myeloid-derived suppressor cells (MDSCs) that contribute to suppression of antitumor immunity and correlate with poor prognosis.³ Reprogramming tumor-associated macrophages (TAMs) from M2 to M1 phenotype represents a potential strategy to enhance antitumor immunity. ST101 is a novel peptide antagonist that prevents C/EBP β dimerization and inhibits C/EBP β -dependent gene expression. Confirmed responses in melanoma and other tumors prompted evaluation of ST101 impact on macrophage differentiation.

Methods Primary human macrophages were cultured from peripheral blood mononuclear cells (hPBMCs) and activated toward the M1 or M2 phenotype by LPS and IFN γ (M1) or IL-4 (M2), respectively, in the presence of ST101. Macrophage M1 (CD80, CD86) and M2 (CD163, CD206) expression were analyzed by flow cytometry and rtPCR. Paired biopsy tissue from the ST101 Phase 1-2 clinical study in patients with advanced unresectable and metastatic solid tumors were collected during screening (prior to ST101 exposure) and within 24 hrs of ST101 administration during cycle 2 of therapy. Nanostring gene expression analysis was performed to determine differential gene expression and the impact of ST101 on the tumor microenvironment.

Results Treatment with pharmacologically relevant concentrations of ST101 (2.5, 5 or 10 μ M) resulted in dose-dependent reduction in M2+ macrophage and corresponding induction of M1+ macrophage. At the highest ST101 concentration, a 12-fold reduction in the M2 to M1 ratio was observed without substantial impact on cell viability. Paired patient biopsy tissue from the ST101 Phase 1-2 clinical study indicates a decrease in C/EBP β target gene IL-6 signaling, an important driver of the M2 macrophage phenotype. Decreased IL-6 signaling resulted in an increase in the tumor-infiltrating macrophage vs. tumor-infiltrating lymphocyte (TIL) ratio, and a decrease in the regulatory T cell (Treg) vs. TIL ratio in tumor samples of treated patients.

Conclusions Overall, these results validate the potential of ST101 in reprogramming M2 macrophages to M1, support a novel, macrophage-driven mechanism of action for ST101 as an anticancer agent and support future exploration of ST101 in immune-oncology therapeutic strategies.

Trial Registration ClinicalTrials.gov Identifier: NCT04478279

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Ethics Approval ST101 study sites all have obtained ethics approval prior to study start. All participants gave consent prior to starting the study. Advarra's IRB Organization (IORG) Number is 0000635; Columbia University Medical Center Institutional Review Board FWA# 00002636; North East – Newcastle & North Tyneside 1 Research Ethics Committee DUKE UNIVERSITY HEALTH SYSTEM Institutional Review Board for Clinical Investigations.

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