ST101, an Inhibitor of the Transcription Factor C/EBPβ, Promotes an Immune-Active Tumor Microenvironment in a Window of Opportunity Study of Patients with Glioblastoma

Fabio Massaiti Iwamoto[1]; Franco Abbate[2], Claudio Scuoppo[2], Clara Levrero[1], Eyal Shaich[3], Robin Arthur Buerki[4,5], Osama Al Dalahmah[1], Abi Vainstein Haras[2] and Jim Rotolo[2]

Affiliations 1. Columbia University, New York, NY; 2. Sapience Therapeutics Inc, Tarrytown, NY; 3. Bioforum, Rehovot, Israel; 4. Northwestern University, Northwestern Medicine Chicago; IL, 5. Northwestern Medicine Cancer Center, Warrenville, IL

Background

The transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) is a master regulator of mesenchymal transformation in GBM (Carro, 2010) and its expression inversely correlates with outcomes (Homma, 2006). Further, C/EBPβ is required for maintenance of immunosuppressive tumor-associated macrophage (TAM) and microglial populations. TAMs may constitute as much as 50% of tumor bulk in GBM and promote tumor progression. ST101 is a first-in-class C/EBPβ antagonist, demonstrated ability to cross an intact blood-brain-barrier (BBB) and promotes selective tumor cell death without impacting normal cell viability (Darvishi, 2022). In ex vivo studies, ST101 results in a 40-fold increase in the M1:M2 macrophage ratio, indicating ability to repolarize immunosuppressive M2 macrophage toward immune-active M1 lineage (Fig. 2). Similarly, ST101 repolarizes microglial cells from an M2-like to M1-like phenotype (Fig. 3). In a Phase 2 clinical study in recurrent GBM (rGBM) (NCT04478279), weekly administration of ST101 resulted in 30% DCR with 2 PR and 7 SD (median duration of stable disease of 6 months; Fig. 4). We designed a window of opportunity study to assess the effect of ST101 on clinical outcomes and pharmacodynamic biomarkers in the neoadjuvant and adjuvant setting in newly diagnosed (ndGBM) and recurrent (rGBM) patients.

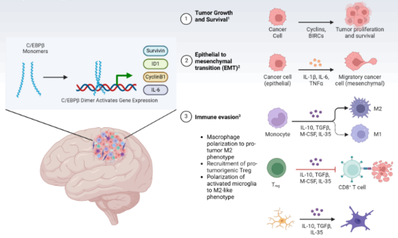


Figure 1: C/EBPβ has an essential role in GBM tumor microenvironment. ST101 antagonizes C/EBPβ transcriptional activity. Non-clinical data support both direct anti-tumor activity and remodeling of the tumor microenvironment to support enhanced immune activity following ST101 exposure.

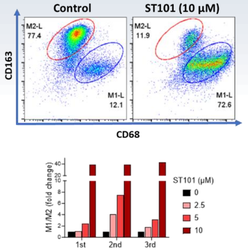


Figure 2: ST101 increases the M1/M2 ratio in human macrophages. (Top) Plots of human PBMC-derived macrophages incubated in media containing IL-4 to drive M2 polarization and ST101. M2-like populations (red) are gated as $CD68^{low}CD163^{high}$, M1-like populations (blue) are $CD68^{high}CD163^{low}$. (Bottom) M1/M2 population ratios for three donors at the indicated ST101 concentrations on Day 10.

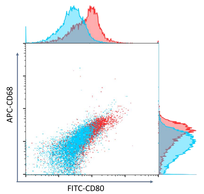


Figure 3: ST101 induces repolarization of human microglia to an M1-like phenotype. Human microglia in culture demonstrate characteristics of immunosuppressive M2-like cells ($CD80^{low}$). Exposure to ST101 shifts the population to demonstrate characteristics of immune active M1-like cells ($CD80^{high}$), suggesting that ST101 repolarizes microglia to an immune activating phenotype, similar to its impact on macrophage.

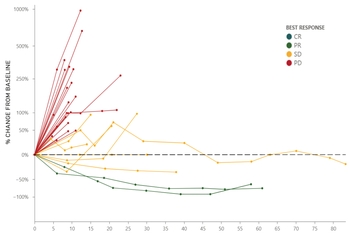


Figure 4: ST101 demonstrated proof-of-concept activity in GBM. Swimmer plot indicating % change in tumor growth from baseline for 30 evaluable GBM patients in Phase 2 clinical study evaluating ST101. Green lines indicate partial response (PR) according to modified RANO criteria (>50% decrease in volume compared to baseline); yellow indicates stable disease (SD) and red indicates disease progression (PD).

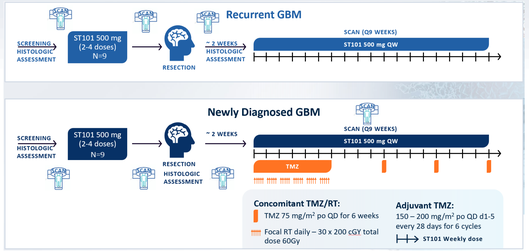
Study Design

The study enrolled 18 GBM patients (9 ndGBM and 9 rGBM) who were candidates for surgical resection. Patients received 2-4 doses of IV 500 mg ST101 QW neoadjuvant prior to surgery. Following surgery, patients continued with ST101 QW + TMZ + Radiation (ndGBM) or ST101 as monotherapy (rGBM). MRI assessments were conducted at screening, post ST101 neoadjuvant and before surgery, after surgery, and every 9 weeks thereafter. Main inclusion/exclusion criteria:

- Newly diagnosed GBM patients who underwent a suboptimal resection and did not receive any treatment for their disease
- Recurrent GBM patients who are candidates for surgery

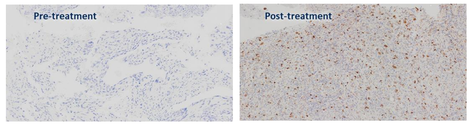
The objective of this study was to assess the effect of treatment with ST101 on tumor tissue and clinical outcomes, as well as assessment of biomarkers in tumors and blood.

Figure 5 – Study Design



Tumor Uptake and Target Engagement

ST101 Detection by IHC



C/EBPβ Immunostaining Decreases with ST101 Treatment

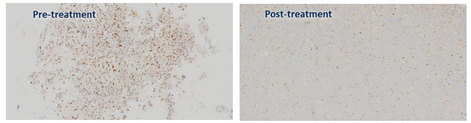


Figure 6: ST101 tumor uptake and target engagement in GBM patients. GBM tissue was collected from suboptimal resection prior to study and surgical resection following 2-4 doses of ST101 from 10 patients. Immunohistochemistry analysis indicates passage through the BBB and tumor uptake (top; ST101 indicated by brown stain) and target engagement, evidenced by decreased C/EBPβ staining following ST101 exposure (bottom; C/EBPβ expression indicated by brown stain) in GBM tumor tissue resected from a patient from study ST101-101. Nuclei counter-stained with hematoxylin and appear blue.

Clinical Results

Newly diagnosed GBM

Clinical outcome of the nine patients with ndGBM, shows 87.5% post-surgery disease control rate (DCR) with one complete response (CR) and six stable diseases (SD) (assessment performed from post-surgery MRI as a baseline) out of eight evaluable patients. As of October 25, 2024, 8/9 patients remain on study, with a median treatment duration of 9.5 months (Fig 7). Progression free survival and overall survival analyses remains ongoing.

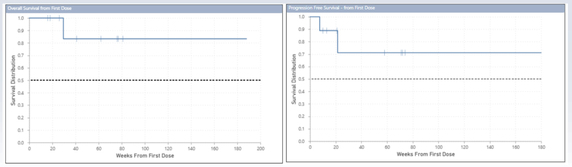


Figure 7: Kaplan Meier Plots for Newly diagnosed GBM. (Left) Overall survival (OS) and (Right) progression free survival (PFS) for ndGBM cohort (n=9).

Recurrent GBM

Clinical outcome of the nine patients with rGBM shows a DCR of 44%, with two partial responses (PR) and two SD. As of October 25, 2024, duration of response (DOR) was greater than 1 year in 2/9 patients. Progression free survival is 3.1 months; overall survival analyses remains ongoing.

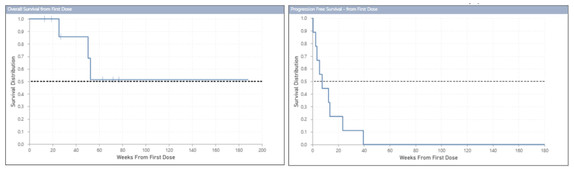


Figure 7: Kaplan Meier Plots for recurrent GBM. (Left) Overall survival (OS) and (Right) progression free survival (PFS) for rGBM cohort (n=9).

Safety

- ST101 is safe and well tolerated
- Injection related reactions present during the infusion and are managed with pre-medication and infusion time changes
- G1-G2 creatinine increases were observed and are managed by dose holidays; no G3 events were reported
- The addition of ST101 to Stupp protocol (TMZ and radiation) in the newly diagnosed patients did not show any increase of the toxicity
- ST101 treatment safety profile allows patients to continue their daily activities

Multiplexed Immunohistochemistry

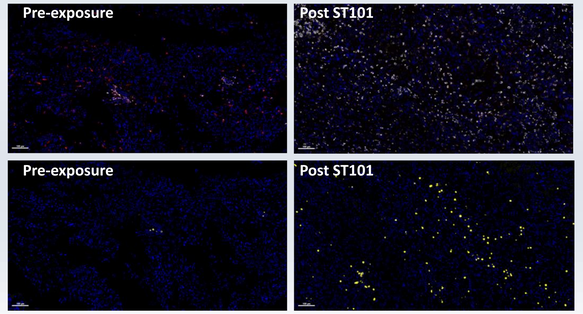


Figure 8: ST101 promotes an immune-active TME in GBM tissue. GBM resections collected prior to and after 2-4 doses of ST101 were analyzed by multiplexed IHC to assess components of the tumor microenvironment. Images indicate macrophage and T cell changes observed in a representative patient with stable disease (SD). (Top) ST101 exposure resulted in reduced M2 macrophages (CD163+; red) and increased M1 macrophages (CD68+; white). (Bottom) ST101 exposure resulted in increased CD8+ T cells (yellow).

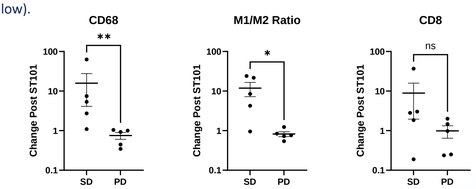


Figure 9: Increased M1/M2 ratio and CD8 T cell infiltration observed in responders to ST101. Quantification of changes in cells positive for CD68, CD68/CD163 and CD8 stratified by response as determined by mRANO (n=10 patients, including n=5 patients with SD and n=5 patients with progressive disease (PD).

Conclusions

- ST101 demonstrated proof-of-concept activity and safety in a Phase 2 and WoO study in GBM.
- ST101 tumor uptake and C/EBPβ target engagement were demonstrated by IHC
- Increases in M1 macrophages in the tumor, M1/M2 macrophage ratio, and CD8+ T cell infiltration correlate with ST101 efficacy.
- These data support combination treatment with ST101 to overcome the resistance to I/O agents observed in GBM.

Contact information: Dr. Jim Rotolo jrotolo@sapiencetherapeutics.com

Abbreviations: AE = adverse event; C/EBPβ = CCAAT/enhancer-binding protein β; CNS = central nervous system; DCR = disease control rate; GBM =glioblastoma multiforme; IHC = immunohistochemistry; iPS = induced pluripotent stem; IRR = infusion-related reaction; IV = intravenous; MGMT = O(6)-Methylguanine-DNA-methyltransferase; mRANO = modified Response Assessment in Neuro-Oncology; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PFS = progression-free survival; PR = pathological response; QW = once weekly dosing; rGBM = recurrent GBM; RP2D = recommended phase 2 dose; SD = stable disease; TMZ = temozolomide.