Neoadjuvant treatment with monotherapy ST101, a C/EBPβ antagonist, results in pathological and clinical responses in glioblastoma patients. Tissue-based analysis and clinical outcomes from a surgical window of opportunity clinical trial

Fabio Massaiti Iwamoto[1]; Abi Vainstein Haras[2], Jim Rotolo[2], Clara Levrero[1], Anastasia Papaioannou[5], Robert Michel[3]; Nicolas Kostelecky[4], Osama Al Dalahmah[1], Robin Arthur Buerki[4,5]
Affiliations 1. Columbia University, New York, NY; 2. Sapience Therapeutics Inc, Tarrytown, NY; 3. Bexon Clinical Consulting LLC, Upper Montclair, NJ; 4. Northwestern University, Northwestern Medicine Chicago, IL, 5, Northwestern Medicine Cancer Center, Warrenville, IL

SAPIENCE THERAPEUTICS

Background

The transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) is a master regulator of mesenchymal transformation in GBM (Carro, 2010) and is required for maintenance of immunosuppressive tumor-associated macrophage (TAM) 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, which promotes selective tumor cell death without impacting normal cell viability (Darvishi, 2022). In preclinical studies, ST101 demonstrated crossing through an intact blood-brain-barrier (BBB) and significantly impacted GBM tumor growth. 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macrophage ratio, indicating ability to repolarize immunosuppressive M2 macrophage toward immune-active M1 lineage (unpublished data). Similarly, ST101 induced repolarization of glial cells from an M2-like to M1-like phenotype. In an ongoing phase 1/2 clinical study in recurrent GBM (rGBM) (NCT04478279), ST101 weekly administration resulted in 30% DCR with 1 PR and 8 SD, (median duration of stable disease of 6 months). 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 GBM (ndGBM) and rGBM.

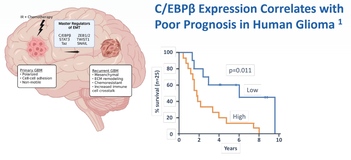


Figure 1: C/EBPβ has an essential role in GBM development. C/EBPβ was identified as a master regulator of mesenchymal transition in GBM (Carro et al., Nature 2010). The mesenchymal state is associated with increased invasiveness and chemoresistance. C/EBPβ expression was also shown to correlate with prognosis in human glioma (Homma et al., Oncology Reports 2006). Patients were stratified according to C/EBPβ expression in resected tumors, as determined by immunohistochemistry.

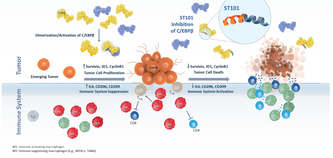


Figure 2: Depiction of the impact of ST101 on C/EBPβ-driven oncogenic and immunosuppressive activity. ST101 antagonizes C/EBPβ transcriptional activity. Non-clinical data support both direct anti-tumor activity and remodeling of the tumor microenvironment to support enhanced immune activity following ST101 exposure.

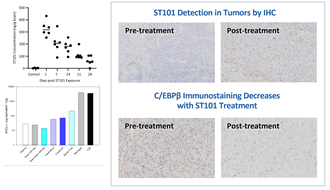


Figure 3: ST101 penetrates the blood brain barrier (BBB). F (Left) Non-clinical data demonstrating ST101 passage thru an intact BBB. Top, ST101 concentrations in naïve C57BL/6 mouse brain tissue at the indicated time post 2 weeks of dosing (3x/weekly via SC injection). Bottom, ST101 brain AUC(0-t) by whole body autoradiography following single ST101 IV injection. Brain:plasma ratio of approx. 1 suggests BBB penetration. (Right) Immunohistochemistry analysis indicates 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.

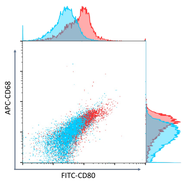


Figure 4: ST101 induces repolarization of human microglia to an M1-like phenotype. Human microglia in culture demonstrate characteristics of immunosuppressive M2-like cells ($CD80^{low}$). Exposure to ST101 shifts the population to demonstrate characteristics of immune active M1-like cells ($CD80^{high}$), suggesting that ST101 repolarizes microglia to an immune activating phenotype, similar to its impact on macrophage.

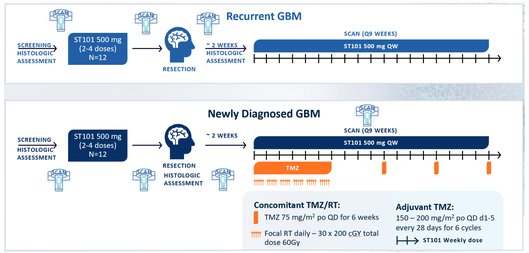
Study Design

The study will enroll approximately 24 GBM patients (12 ndGBM and 12 rGBM) who are candidates for surgical resection. Patients will receive 2-4 doses of IV 500 mg ST101 QW neoadjuvant. Following surgery, patients will continue ST101 QW + TMZ + Radiation (ndGBM) or ST101 as monotherapy (rGBM). MRI assessment will be 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 is 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



Pathological Results

As of November 7, 2023, six patients with rGBM and six with ndGBM received 2-4 doses of ST101 before surgery and were evaluable. At surgery, histopathology of tumor samples from the newly diagnosed patients showed that 3/6 patients had geographic necrosis indicative of treatment effect related to ST101 monotherapy, as these patients were previously treatment naive. This type of necrosis was identified as distinct from pseudopalisading necrosis secondary to tumor growth. All cases with pseudopalisading necrosis also showed geographic necrosis. (Fig 6A Fig 6B).

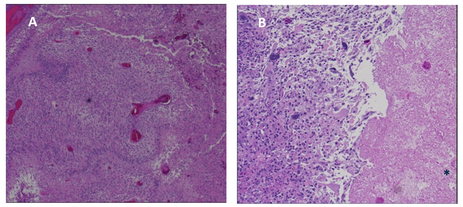


Figure 6: Distinguishing tumor-related necrosis versus treatment-related necrosis. A) Pseudopalisading tumor necrosis in a ndGBM. B) Geographic necrosis following ST101 therapy (*right side) in a ndGBM sample.

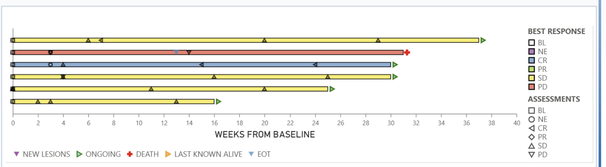
Clinical Results

Newly diagnosed GBM

Clinical outcome of the six patients with ndGBM, shows 83% post-surgery disease control rate (DCR) with one complete response (CR) and four stable diseases (SD) (assessment performed from post-surgery MRI as a baseline). As of November 7, 2023, 5/6 patients remain on study, with a treatment duration of ~15-38 weeks (Fig 7).

Progression free survival and overall survival analyses remains ongoing in this study

Figure 7– Newly diagnosed GBM swimmer plots

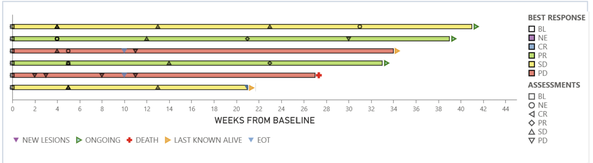


Recurrent GBM

Clinical outcome of the six patients with rGBM shows a DCR of 67%, with two partial responses (PR) and two SD. As of November 7, 2023, 3/6 patients remain on study with disease control beyond 6 months (two PR and 1 SD), resulting in a 6mPFS of 50%. Geographical necrosis was also observed in 5/6 patients in the rGBM cohort following surgical tissue analysis, potentially indicating treatment-related effect of ST101 monotherapy (Fig.8).

Progression free survival and overall survival analyses remains ongoing in this study.

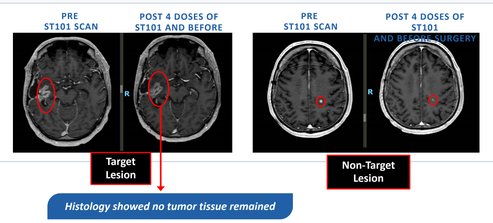
Figure 8 – Swimmer Plot Recurrent GBM Cohort



Case Study

A case study of a patient with rGBM with a fully necrotic tumor upon surgical resection can be seen in figure 9. A patient with right temporal recurrency along with a non-target lesion in the left hemisphere with associated clinical progression received neoadjuvant treatment with ST101 (QW x 4 wks) and then underwent resection of the right temporal lesion. The patient exhibited clinical improvement and a scan following neoadjuvant treatment (prior to surgery) showed stability of the temporal recurrence and improvement of left hemisphere lesion. Pathological review of resected tissue showed gliosis with significant treatment effect and tumor tissue was not found.

Figure 9 – Patient's MRI before and after Neoadjuvant ST101



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

Conclusion

- Newly diagnosed GBM patients treated with neoadjuvant and adjuvant ST101 as part of their standard of care treatment, had 83% DCR including 1 CR in six patients
- Recurrent GBM patients treated with neoadjuvant and adjuvant ST101monotherapy, had 67% DCR including 2 PR in six patients
- Extensive treatment-related effects (geographical necrotic tissue) were observed in GBM patients treated with neoadjuvant ST101 monotherapy, including patients who were previously treatment-naïve

Special thanks to:
- ***Patients and their families***
- ***The Ben and Catherine Ivy Foundation Emerging Leaders Award (FI), who partially funded this trial***

Contact information: Dr. Abi Vainstein-Haras abi@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.