Clinical and Biological Activity of ST101, a Peptide Antagonist of C/EBPß, in Recurrent Glioblastoma (rGBM) Patients
Results From the rGBM Cohort of a Multi-Cohort Phase 2 Study

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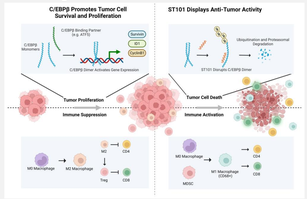
SAPIENCE THERAPEUTICS

Background

- ST101 is a first-in-class peptide antagonist of CCAAT/enhancer-binding protein β (C/EBPβ) that promotes selective tumor cell death in multiple cancers without impacting normal cell viability (Fig 1.)
- C/EBPβ is a master regulator of mesenchymal transformation in GBM[1]
- C/EBPβ has been proposed as a master regulator of the immuno-suppressive M2 program in macrophages
- In vitro, ST101 has been shown to induce a shift in PBMC-derived macrophage and human iPS-derived microglia, resident macrophage of the CNS, from an M2-like immunosuppressive phenotype toward an immune-active M1-like identity (Fig. 1)[2]

Fig 1. ST101 Mode of Action

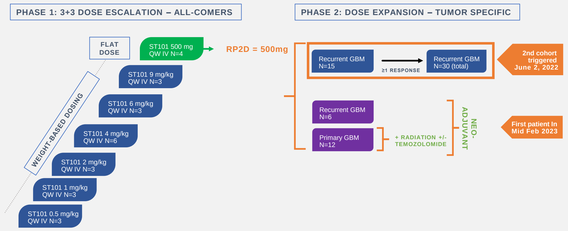


Study Design

- ST101 is being evaluated in a Phase 1/2 clinical study in patients with advanced unresectable and metastatic solid tumors, with an expansion cohort in rGBM
- The rGBM cohort showed ≥ 1 response in the first 15 patients, triggering the criteria to expand to a total of 30 patients
- Patient population: patients with PD/recurrence after standard 1st line treatment*
- Treatment: monotherapy ST101 500 mg, IV, QW
- Primary objective: evaluate the safety/tolerability of ST101 and assess efficacy parameters: ORR, DCR, PFS at 6 months and OS
- MRI was performed every 9 weeks and response assessed by mRANO

*Surgery, radiation, TMZ.

Fig 2. Design of Study Phases 1 and 2



Results

ST101 Efficacy (n=30)

- 33 patients had been enrolled - 30 were evaluable for efficacy
- Clinical activity observed in 9 patients (30% DCR): 1 patient with a PR for 54 weeks (Fig. 3) and 8 patients with SD (median of 5 months)
- As of September 25, 6-month and 9-months OS of 73% and 52%, respectively
- Two patients with SD remain on treatment; therefore, 6-month PFS and all OS evaluations remain ongoing
- Median OS cannot be assessed at the time of this data cut

Fig 3. Current Status of rGBM Patients

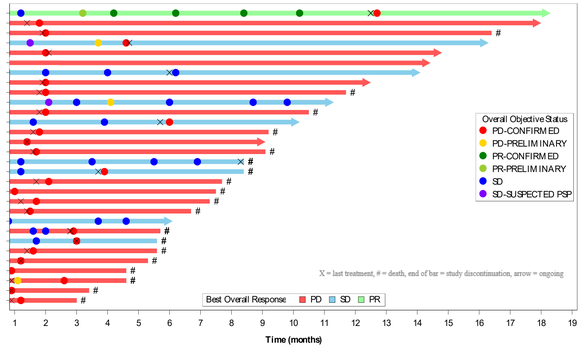
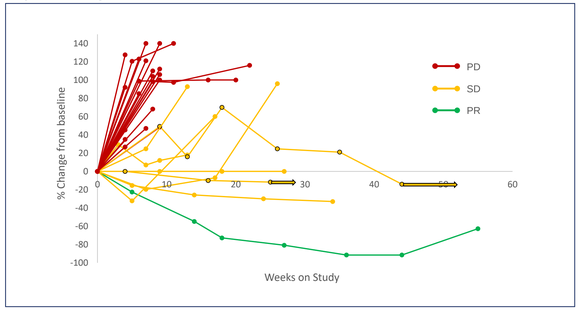


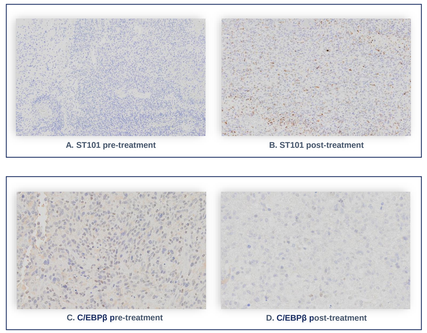
Fig 4. Change in Tumor Volume Over Time in rGBM Patients



ST101 Crosses the Blood Brain Barrier

- A sub-study of ST101-101 provides rGBM patients ST101 in the neoadjuvant setting
- Pre- and post-ST101 treatment surgical tissue from the sub-study was made available for analysis
- At 6 weeks of treatment, IHC analysis of rGBM biopsies demonstrated:
  - ST101 uptake by tumor cells, as indicated by red stain (Fig. 5A & B)
  - ST101 target engagement by reduced C/EBPβ expression (Fig. 5C & D)

Fig 5. Detection of ST101 and C/EBPβ by IHC and Immunostaining



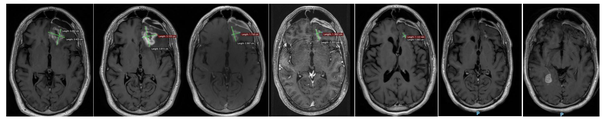
Case Study 1: ST101 Pathological Response

- Left frontal recurrence on MRI 30 months after initial diagnosis; clinically asymptomatic
- After 9 QW doses, patient remained asymptomatic, but MRI showed increase of the enhancing area; follow up MRI showed stabilized disease under ST101 treatment
- At week 22, patient remained asymptomatic, but MRI showed further enlargement
- Based on the MRI, patient considered progressed, came off study and underwent surgical resection
- Pathology showed necrosis (~90%) and scattered atypical cells (~10%)
- Current status: >9 months remission since ending ST101

Case Study 2: ST101 MRI (mRANO) Response

- 34 y/o male patient; IDH R132H positive, MGMT partial methylation
- Diagnosed June 2021; resection followed by TMZ + radiation
- Disease recurred November 2021; second resection
- Enrolled Jan 2022, last dose Feb 7th 2023

Fig 6. GBM patient with durable PR



Baseline	+14%	-59%	-71%	-93%	-93%	New lesion
12/28/2021	2/22/2022	4/25/2022	5/24/2022	9/28/2022	11/23/2022 (Week 44)	2/7/2023 (Week 55)

ST101 Safety

- ST101 was safe and well tolerated: IRRs were the most frequently reported AE
- IRRs were managed by pre-medication (antihistamines and leukotriene antagonist) and infusion rate adjustment
- Infusion tolerance increased over time with 79% of patients experiencing IRRs during the first infusion, which dropped to 21% experienced by the eighth infusion
- Creatinine increases grade 1-2. No grade ≥ Grade 3 events

Conclusion

- ST101 demonstrates ability to pass through the blood-brain-barrier and engage C/EBPβ (Fig. 5)
- Single agent ST101 demonstrated clinical activity and tissue treatment effect
- This data snapshot also demonstrated that patients receiving ST101 monotherapy exhibited encouraging response and survival outcomes
- Results from the ST101-101 study warrants further assessment of ST101 as part of a combination treatment approach for patients with rGBM

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References: 1. Carro et al. Nature 2010;463(7279):318–325. 2. Darvishi et al. Mol Cancer Ther. 2022;21(11):1632–1644.

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.