2024 ASCO® ANNUAL MEETING

Efficacy and biomarker analysis of phase 2 and window-of-opportunity cohorts of patients with glioblastoma treated with ST101, an inhibitor of the transcription factor C/EBPβ

Clinical Science Symposium – Advancing Trial Design:
Illuminating Tumor Evolution in Central Nervous System Cancer

June 1st 3:00PM- 4:30 PM

Fabio Iwamoto, Abi Vainstein-Haras, Jim Rotolo, Clara Levrero, Eyal Shaich, Osama Al Dalahmah, Robin Buerki

ST101: Well-Tolerated Potential Treatment Option for Patients with GBM

Clinical Outcomes from 3 Cohorts of Patients

- **Main study: monotherapy in recurrent GBM, n=30**
  - 2 PRs
  - 7 SD
  - 53% 9-mo O/S; 40% 12-mo O/S
- **Window of Opportunity (WoO) Study:**
  Monotherapy in recurrent GBM, n=6
  - 2 PRs (1 unconfirmed), 1 ongoing
  - 2 SD, 1 ongoing
  - Median OS ~12 months
- **Window of Opportunity Study:**
  Combination in newly diagnosed GBM, n=6
  - Combination w/ Stupp protocol
  - Safe and no overlapping toxicity
  - 5/6 patients alive (25-57 wks)

Biomarker Data from WoO Cohorts

- **ST101 crosses the BBB and penetrates tumor**
- **Target (C/EBPβ) engagement and degradation**
- **Modulation of the tumor immune microenvironment to promote anti-tumor activity:**
  - Increase CD8+ T cell infiltration
  - Change of polarization of macrophages from immune-suppressive M2-type to immune-active M1-type

ST101 is a Protease-Stable, Peptide Antagonist of C/EBPβ

First Molecule of a New Class of Stable Peptides, SPEARs, to Enter the Clinic

SPEARs

Stabilized Peptides Engineered Against Regulation

Properties	Typical Peptides	SPEARs
Protease Stable	No	Yes
Half-life	Minutes	Days
Immunogenic	Possible	No
Cell Permeable	No	Yes
Blood-Brain Barrier Permeability	No	Yes

ST101:C/EBPβ Antagonist

PPI Disrupting Domain

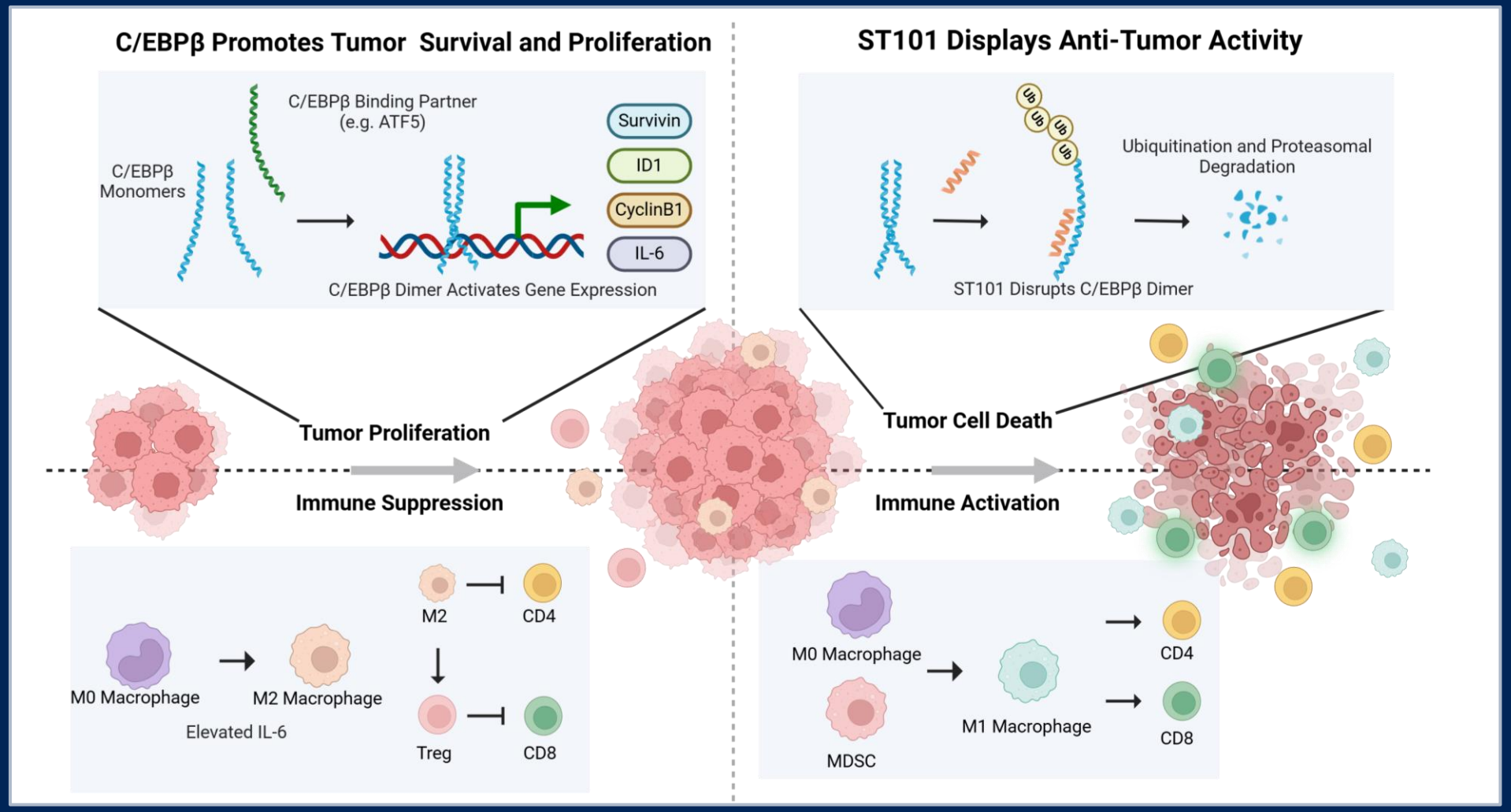
Cell Penetrating (CP) Domain

- 38-residue synthetic peptide composed entirely of D-amino acids
- Molecular weight of 4.724 kDa
- CP domain delivers peptide to nucleus
- PPI domain enables binding to C/EBPβ
- Anti-oncogenic and immune-activating

PRESENTED BY: Fabio Iwamoto, MD

ST101 Antagonizes C/EBPβ Transcriptional Activity

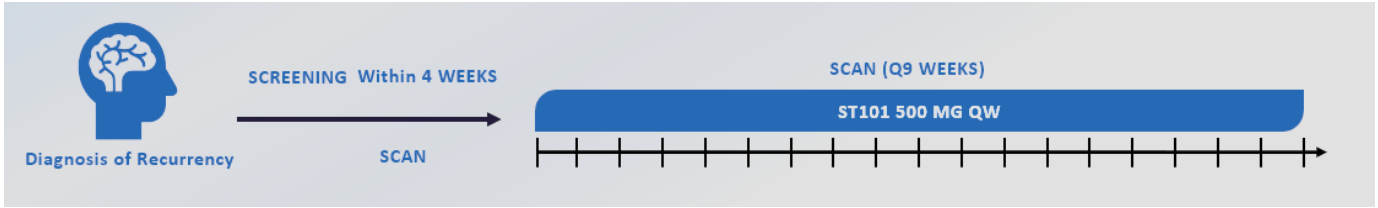
Anti-Tumor Activity and Immune Activation



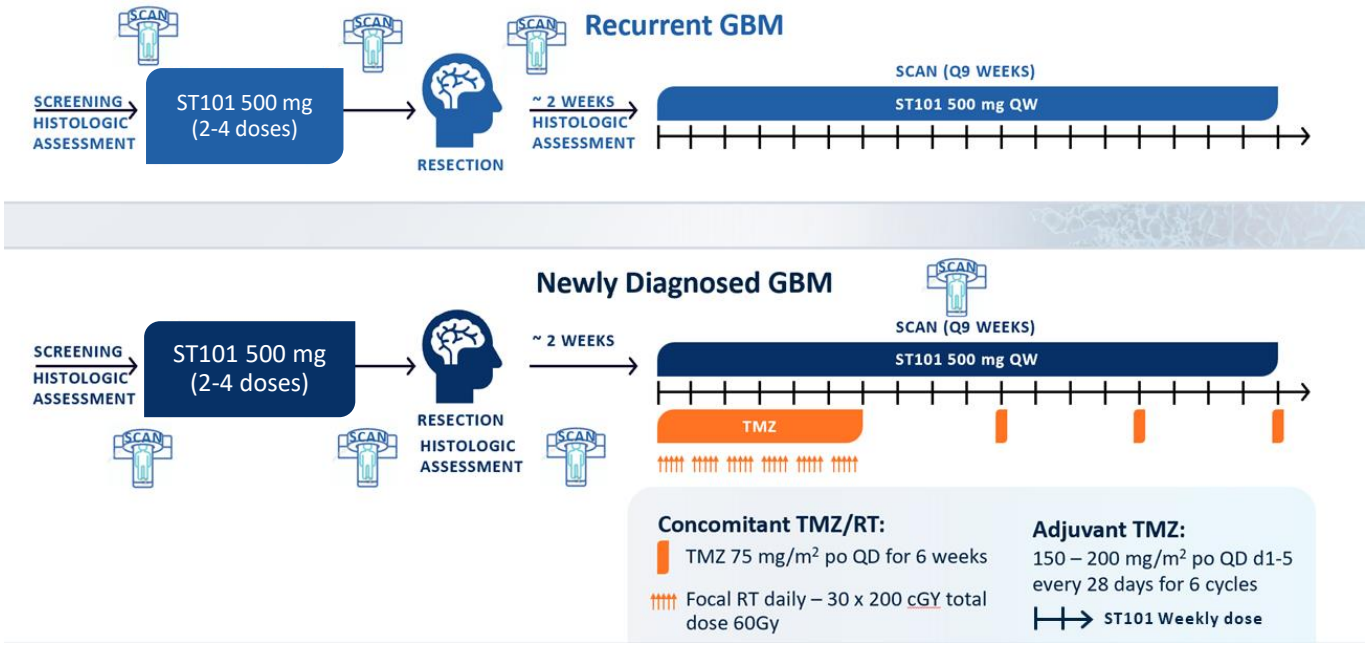
PRESENTED BY: Fabio Iwamoto, MD

ST101 Study Design: Three GBM Cohorts

Main Study- Phase 2 (Expansion)



Study Design – Surgical Window of Opportunity Study



→ **Monotherapy**
- Safety
- Efficacy

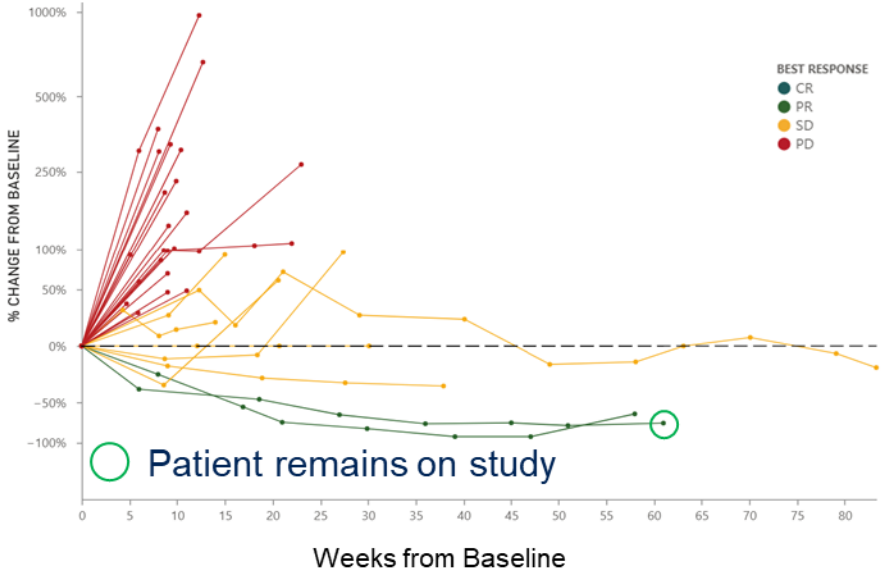
→ **Monotherapy**
- Safety
- Efficacy

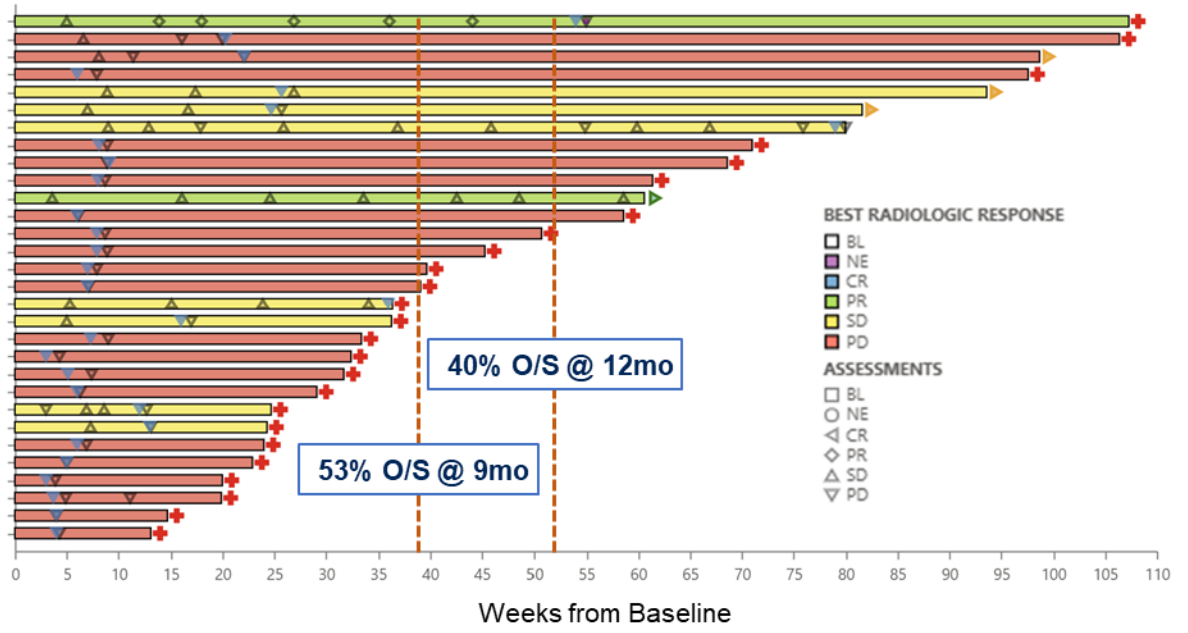
→ **Biomarker Analysis**

→ **Combination with RT/TMZ**
- Safety
- Efficacy

ST101 Monotherapy Phase 2: Results of rGBM Cohort

Ongoing Study, Data Cut May 22, 2024





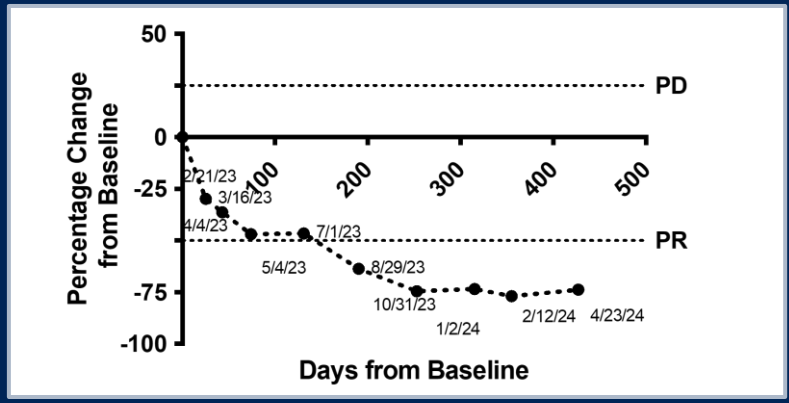
30 Evaluable recurrent GBM Patients

- 2 PR, with median duration ~1yr, 1 remains ongoing
- 7 SD with median duration; treatment range 13-79 wks
- 53% 9-mo O/S; 40% 12-mo O/S

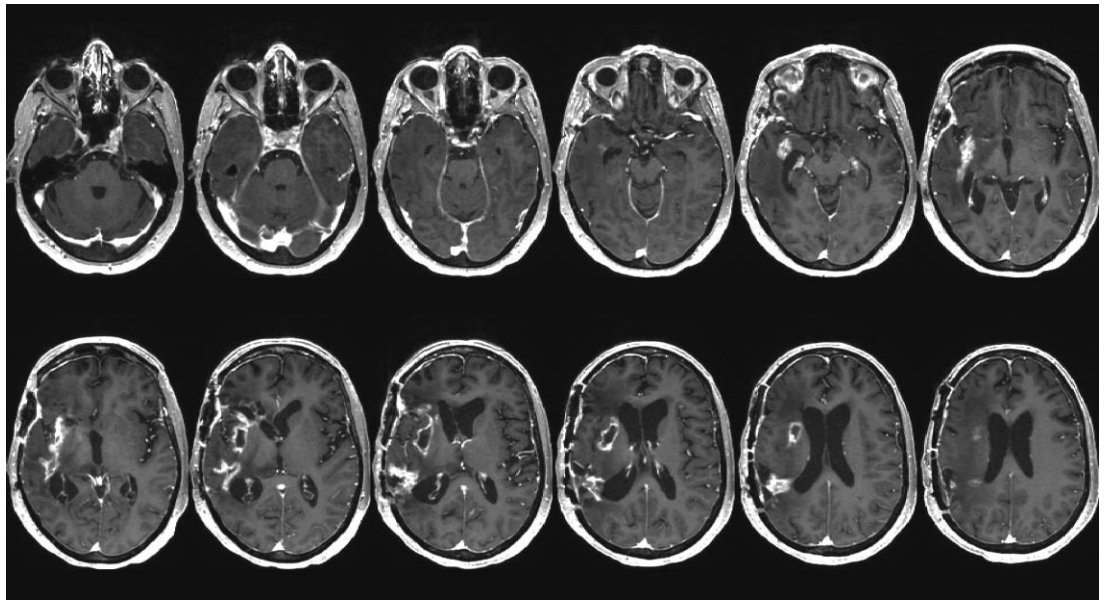
Case Study: Durable PR in 63 yo Woman with GBM

63 yo woman with IDH-wild type unmethylated MGMT promoter GBM

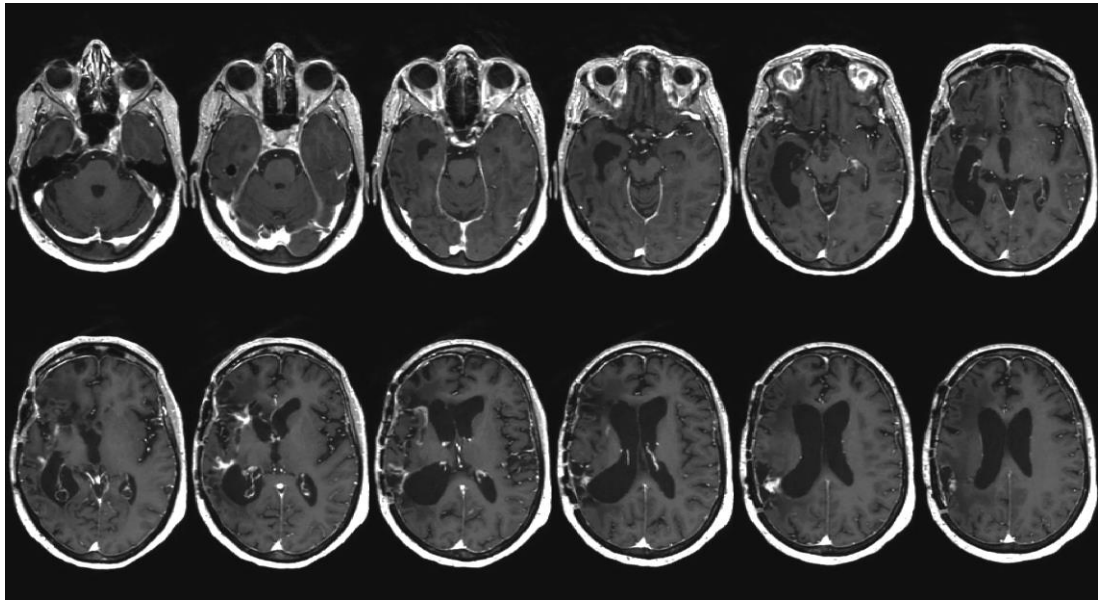
- **Surgery followed by RT/TMZ**
- **Progression 7 months after completion of RT and accrued to ST101 expansion cohort (non-surgical)**
- **Sustained PR and pt continues on treatment**
- **Clinical improvement of hemiparesis**



Baseline



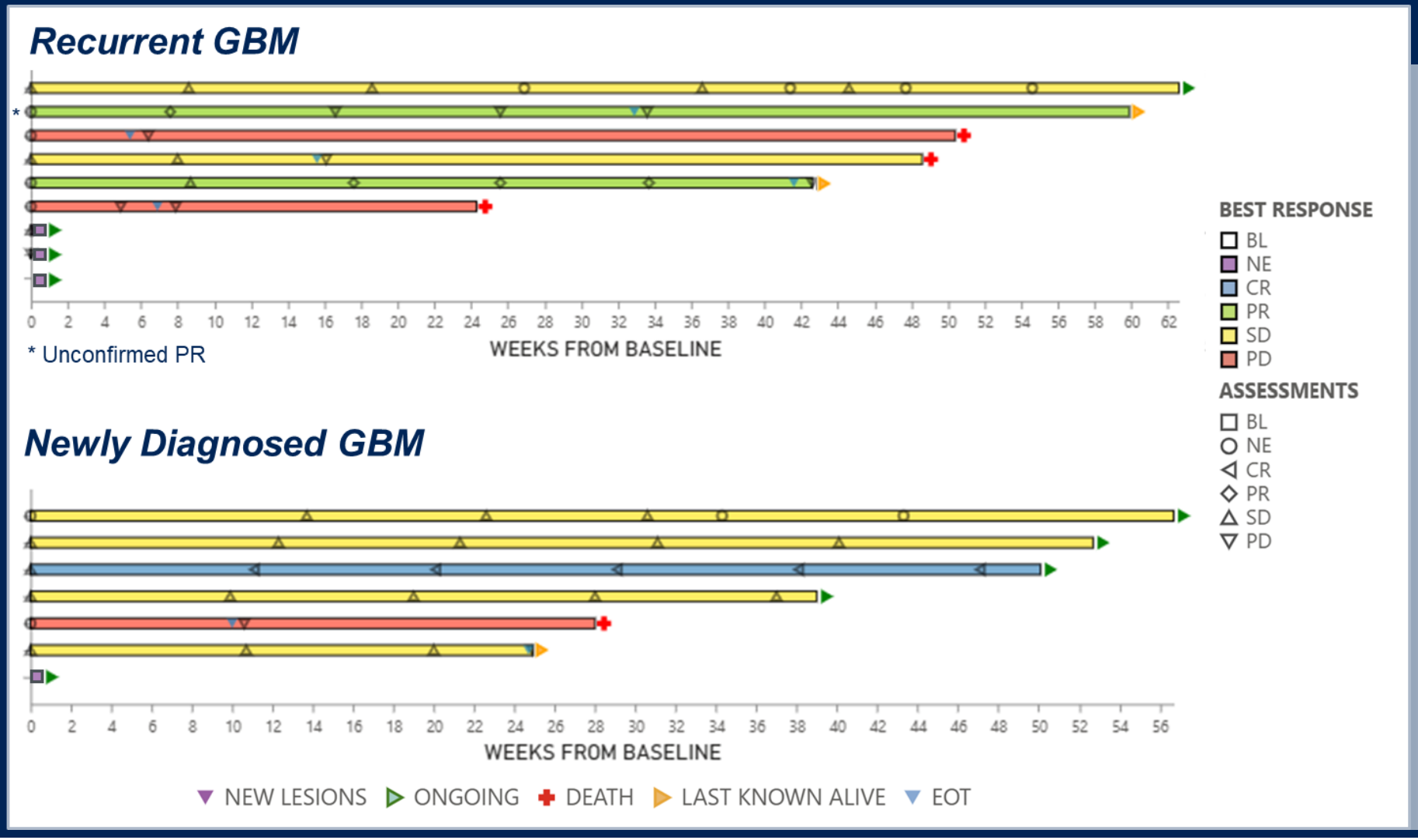
14 months



Co-registered MRI and graphic: courtesy of Dr. Benjamin Ellison (UCLA)

Window of Opportunity Study: Clinical Status

Ongoing Study, Data Cut May 22, 2024



- N=9, 6 evaluable
- 4/6 disease control: 2PR/2SD
- PFS at 6months 50%
- 3/6 patients alive (41-62 wks)

- N=7, 6 evaluable
- 5/6 disease control 24-56+ weeks post surgery
- 5/6 patients alive (25-57 wks)
- No unexpected or overlapping toxicities with the combination of ST101 with SOC

Safety

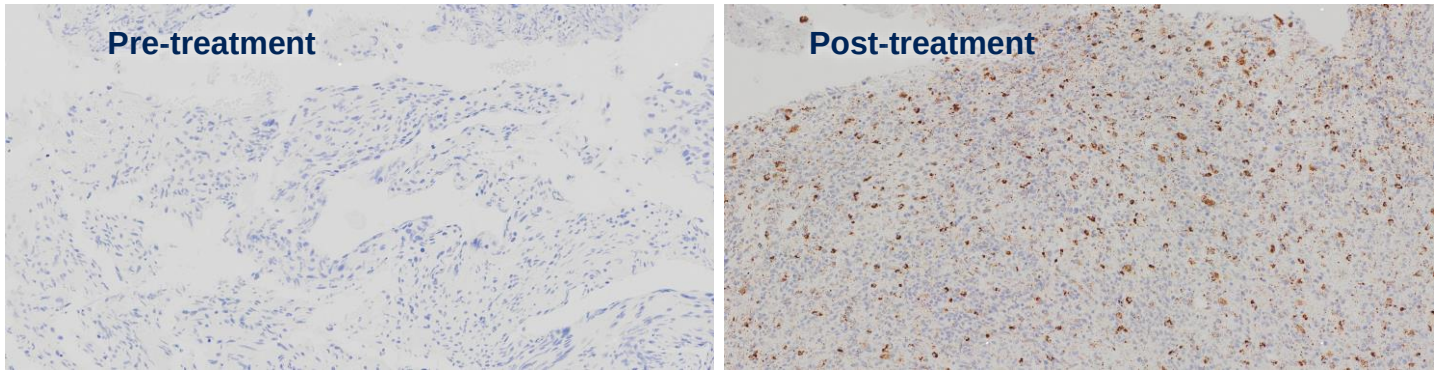
Most common AEs were:

- **IRR –Resolved at the end of infusion, incidence decrease with subsequent infusions**
- **Creatinine increase – Decreased or normalized with drug holidays**

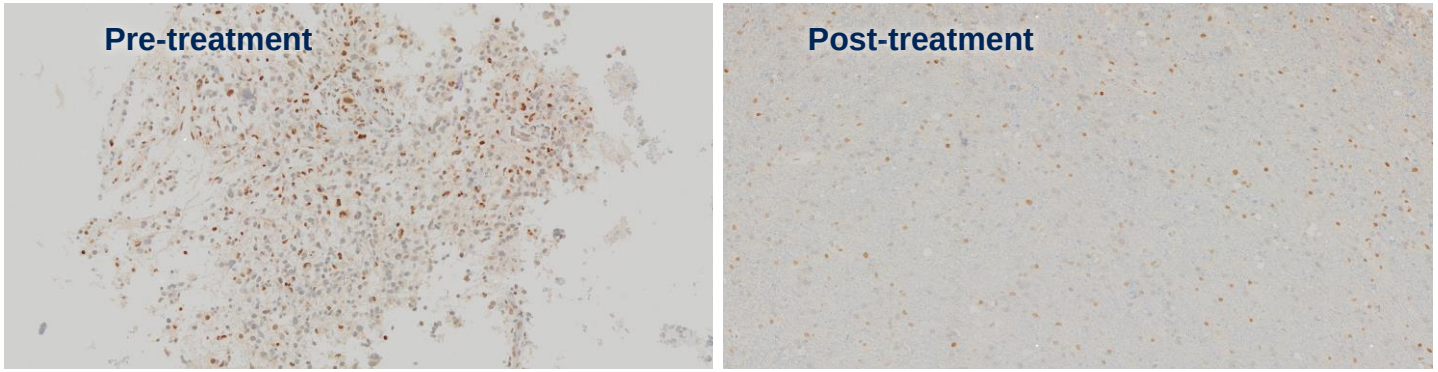
Treatment related AEs >10%	All AEs	≥3
Infusion related reaction	81%	2.5%
Creatinine Increase	35.5%	-
Fatigue	21.5%	-
Nausea	19.8%	-
Pruritus	14.9%	-

WoO Study Demonstrates ST101 Crossing the BBB, Uptake Into Tumors and Target Engagement

ST101 Detection in GBM by IHC



C/EBPβ Immunostaining Decreases with ST101 Treatment

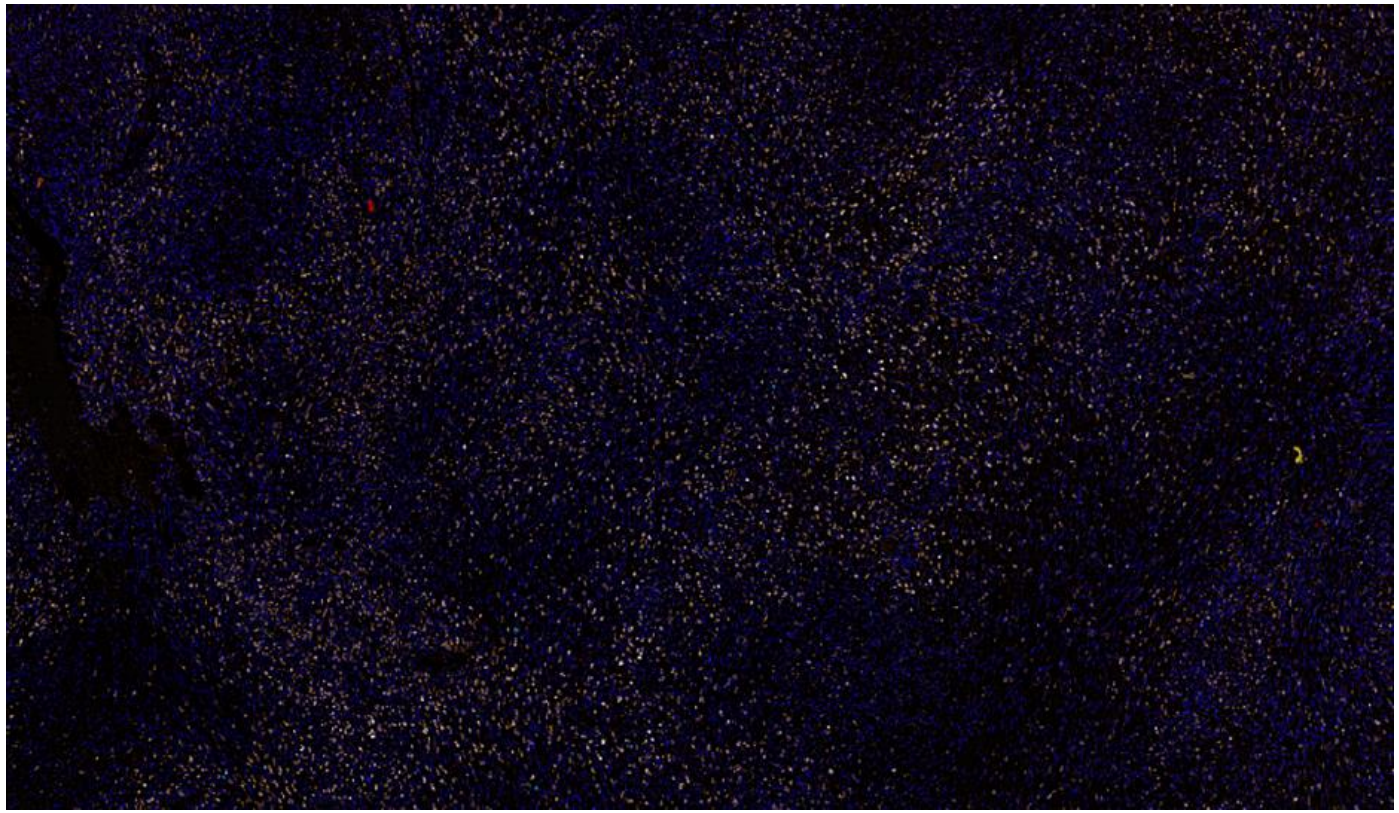


- Tumor tissue before and after 2 doses of ST101 monotherapy in a newly diagnosed GBM patient
- Top panels demonstrate ST101 uptake into GBM using anti-ST101 pAb
- Bottom panels indicate target engagement
  - Upon binding to ST101, C/EBPβ gets ubiquitinated and undergoes proteasomal degradation[1]

[1]Rotolo et al., Molecular Cancer Therapeutics, November 2022

Multiplex IHC Analysis of GBM Tumors Before and After ST101 Exposure

Immune Spatial Profiling of Patients' GBM Tissue



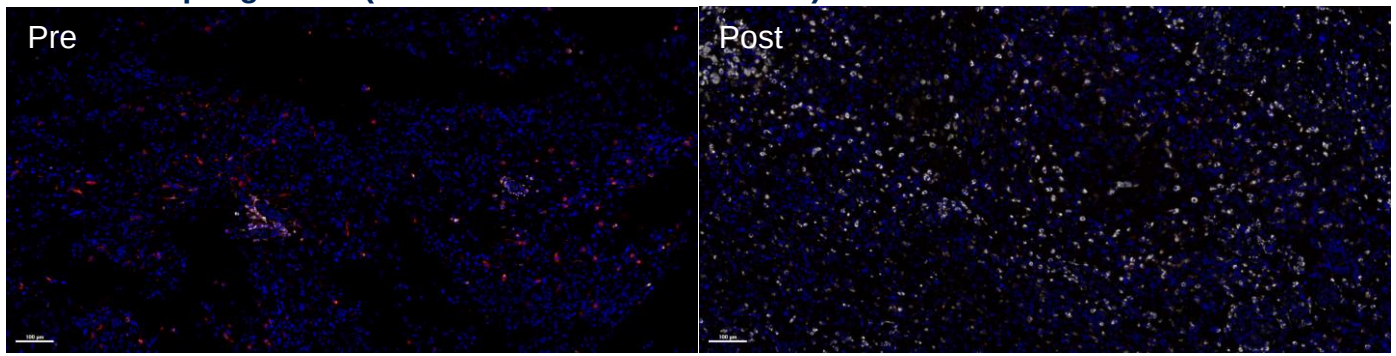
Blue = DAPI, Red = CD163, White = CD68, Yellow = CD8

- Matched biopsies collected from 5 GBM tumors (Pre- and Post-ST101 exposure)
  - 4 patients with stable disease (SD) ranging from 19-52 weeks
  - 1 non-responder
  - ndGBM and rGBM
- Immune cell profiling performed using Macrophage Polarization panel on Akoya PhenoImager Platform

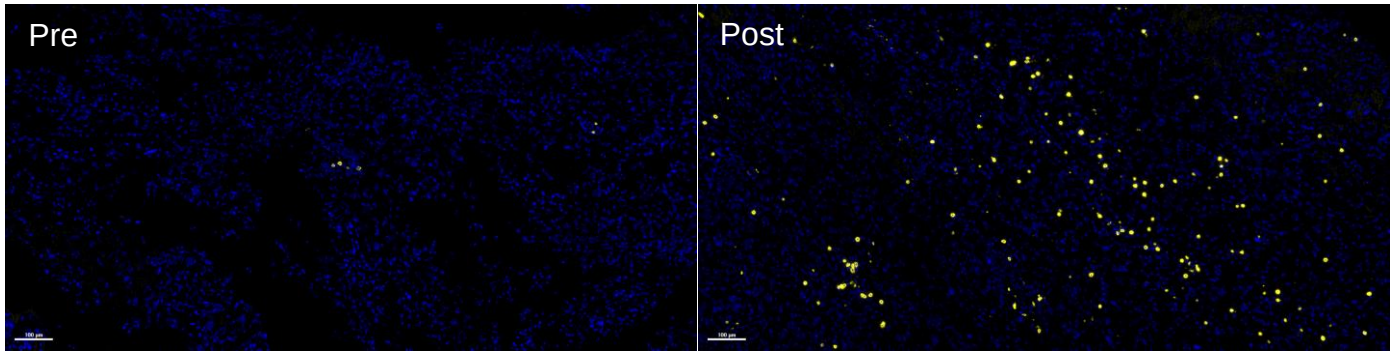
ST101 Increases Macrophage & CD8 T Cell Infiltration into Tumor

Data Suggests Increased M1/M2 Ratio in Tumor-associated Macrophages

ST101 increases tumor-associated macrophages (CD68+) and increases M1/M2 macrophage ratio (CD68+CD163-/CD68+CD163+)

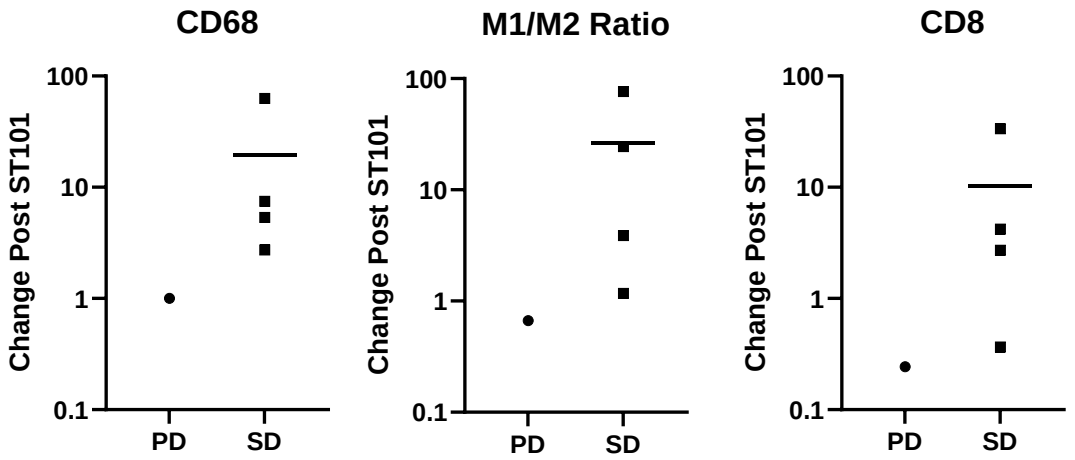


ST101 increases CD8+ T cell infiltration into tumors



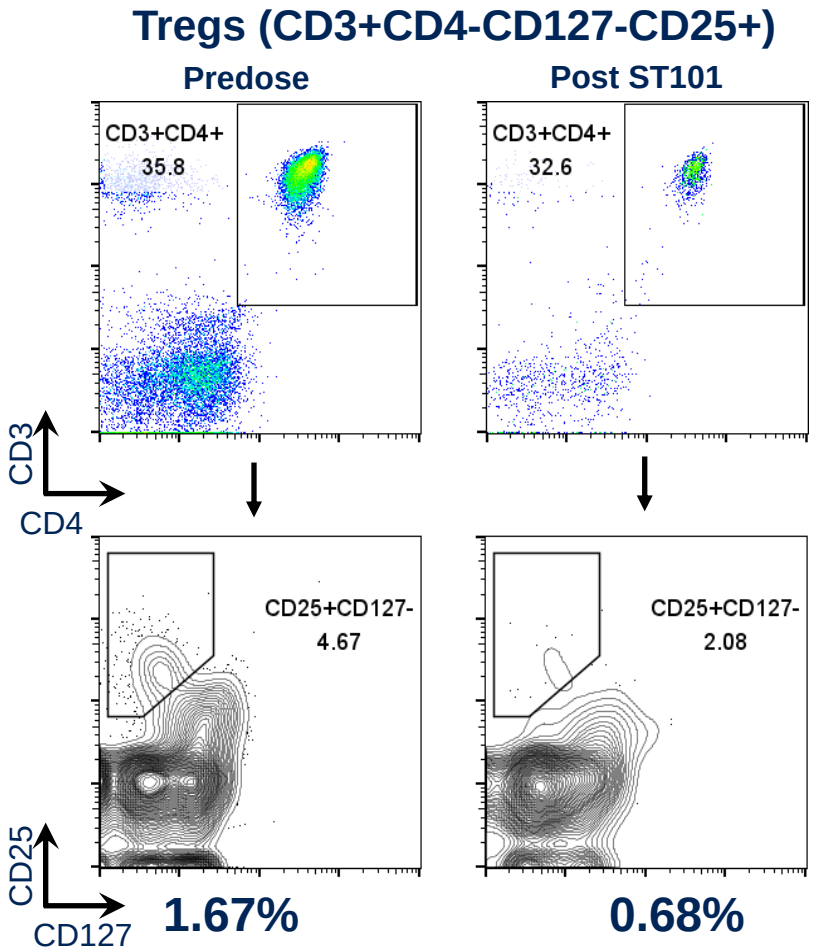
Blue = DAPI, Red = CD163, White = CD68, Yellow = CD8

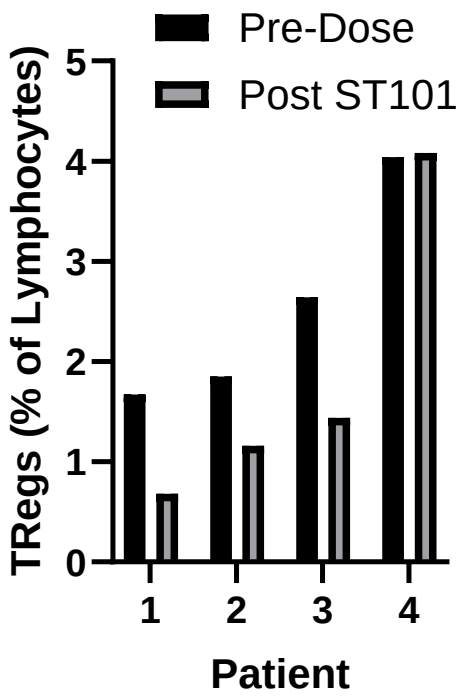
Representative image from patient in newly diagnosed cohort



- CD68 represents total macrophage population
- M1-like cells = $CD68^{+}CD163^{-}$
- M2-like cells = $CD68^{+}CD163^{+}$

ST101 Reduces Immune-Suppressive T_{Regs} in Peripheral Blood of GBM Patients





- **Blood collected prior to ST101 exposure and following the 2nd ST101 dose**
- **Peripheral blood processed and analyzed for lymphocyte and myeloid markers by flow cytometry**
- **Data identifies a decrease in T_{Reg} concentration as a percentage of total lymphocytes in 3 of 4 patients analyzed**

Conclusions and Future Directions for ST101 in GBM

C/EBPβ is a novel target in GBM

ST101 has demonstrated penetration into brain tumor tissue

- C/EBPβ target engagement and degradation
- Modulation of the tumor immune microenvironment
  - Increased CD8+ T cell infiltration
  - Increased macrophage infiltration
    - Shift from immune-suppressive M2-type to immune-active M1-type

ST101 clinical activity and safety

- Durable PRs and SD with monotherapy
- Well tolerated
- Safe in combination with radiotherapy and temozolomide

Analyses of tissue pre- and post-ST101 with snRNAseq and spatial transcriptomics ongoing

Future studies planned in combination with SoC

New data presented supports combination with I/O agents

Acknowledgments

Funding

- Ben and Catherine Ivy Foundation
- William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma at NewYork-Presbyterian Hospital
- Keep Punching Foundation
- P30CA013696 (NIH/NCI Cancer Center Support Grant)
- Sapience Therapeutics

Patients and Families

Columbia University

- Andew Lassman
- Peter Pan
- Maria Diaz
- Aya Haggiagi
- Mary Welch
- Laura Donovan
- Guy McKhann

Northwestern University

- Osaama Khan
- Nicholas Kostelecky

Duke University

- Katie Peters

UCSF

- Nicholas Butowski