Initiation of clinical studies with SL-701, a synthetic multi-peptide vaccine with enhanced immunostimulatory properties targeting multiple glioma-associated antigens, in adults with first recurrence of glioblastoma

John Boockvar, M.D.¹; Imithri Bodhinayake, M.D.¹; Christopher Brooks, Ph.D.²; Janice Chen, Ph.D.²; Jonathan D. Schwartz, M.D.²; Eric Rowinsky, M.D.²; David Reardon, M.D.³

¹ Weill Cornell Medical College, New York, NY, U.S.A.; ² Stemline Therapeutics, Inc., New York, NY, U.S.A.; ³ Dana-Farber Cancer Center, Boston, MA, U.S.A.

Society for Neuro-Oncology Annual Scientific Meeting 2014
Glioblastoma multiforme: a significant unmet medical need

- Glioblastoma multiforme (GBM) is the most frequent malignant primary brain tumor in adults.
- Resection, radiation, and temozolomide confer survival benefit; however median overall survival (OS) remains limited: ~ 15 months.\(^1\)
- Glioma stem cells are resistant to radiation and chemotherapy and thought to be key contributors to tumor recurrence.
- Therefore, a multi-pronged approach targeting both tumor bulk and cancer stem cells is a necessary therapeutic strategy for GBM.
- Immunotherapies have shown promise in many solid tumors, and emerging evidence suggests that the central nervous system is immunocompetent and accessible to immune cells.\(^2\)

SL-701 background

- SL-701 is a synthetic multi-peptide immunotherapy.
  - Consists of three shortened peptides corresponding to targets overexpressed by GBM.
  - Includes peptides of IL-13Rα2 and survivin that have been engineered with amino acid substitutions to increase immunostimulatory activity.
- Most gliomas studied to date express two or three of these targets.\(^3\)
- An earlier version of this therapy was associated with major responses, including durable complete responses (CRs), in advanced brain cancer patients.
- SL-701 has been optimized over this earlier version for enhanced immunostimulation and ease of administration.
- SL-701 peptides are emulsified and administered via s.c. injection; immunostimulants are co-administered to induce maximal activation of the immune system.
- SL-701-0114 clinical trial is currently open and recruiting adult patients with second-line GBM.

\(^3\) Okada, H. et al. J Neurooncol. 2008; 88 (3)
(A-C): Expression of IL-13Rα2, EphA2, and survivin was examined on normal brain and GBM specimen by immunohistochemistry. Adapted from Uematsu, M. et al. and Wykosky, J. et al. \(^4,5\) (D) EphA2 is expressed on GBM stem-like cells. A-172 GBM cells were stained with antibodies to EphA2 and CD133 and analyzed by flow cytometry.

## Previous clinical experience

Earlier version of SL-701, comprised of similar peptides, demonstrated tumor regressions, including durable CRs and partial responses (PRs), in adults with GBM and children with malignant glioma in investigator-sponsored Phase 1/2 trials.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Peptides</th>
<th>Administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients with recurrent high-grade glioma</td>
<td>IL-13Rα2_{345-353:1A9V} EphA2_{883-891} YKL-40_{202-211} gp100_{209-217} PADRE</td>
<td>i.n. injection of peptide-loaded DCs; i.m. injection of poly-ICLC</td>
<td>6</td>
</tr>
<tr>
<td>Adult patients with recurrent low-grade glioma</td>
<td>IL-13Rα2_{345-353:1A9V} EphA2_{883-891} Survivin_{96-104:M2} WT1_{126-134:Y1} Tet_{A830}</td>
<td>s.c. injection of emulsified peptides; i.m. injection of poly-ICLC</td>
<td>7</td>
</tr>
<tr>
<td>Children with malignant glioma</td>
<td>IL-13Rα2_{345-353:1A9V} EphA2_{883-891} Survivin_{96-104:M2} Tet_{A830}</td>
<td>s.c. injection of emulsified peptides; i.m. injection of poly-ICLC</td>
<td>8</td>
</tr>
</tbody>
</table>
SL-701, an enhanced immunotherapy for GBM

SL-701, comprised of IL-13Rα2 variant, EphA2, and survivin variant peptides, has been optimized over earlier version for enhanced immunostimulation and ease of administration.

- Replaced previous survivin peptide with a novel, highly immunogenic mutant survivin peptide.
- T→M substitution in wildtype survivin<sub>95-104</sub> peptide increases binding affinity to HLA and enhances anti-survivin cytotoxic T cell responses.<sup>9</sup>
- Co-administration of imiquimod and GM-CSF immunostimulants employed to synergistically enhance cytotoxic T cell responses.<sup>9</sup>

Mice were immunized s.c. with OVA peptide on days 0 and +7. GM-CSF was applied s.c. with peptide vaccine and 24 h before. A 5% imiquimod (IMQ) cream was applied to the skin at the vaccination site 30 min before and 24 h after vaccination. Splenocytes were isolated on day 14 to test for the presence OVA-specific CD8<sup>+</sup> T cells. Adapted from Hilf, N. et al.<sup>10</sup>

IFN-γ spots / 200,000 cells

T cells from a normal donor were raised against the new Stemline survivin peptide or the survivin peptide used in previous glioma trials.<sup>7,8,9</sup> IFN-γ-secreting cells in response to the corresponding wildtype peptides were enumerated by ELISPOT. Adapted from Bernatchez, C. et al.<sup>9</sup>

Adapted from Bernatchez, C. et al. Vaccine. 2011; 29 (16);<sup>9</sup> Hilf, N. et al. AACR 2010, abstract nr 5623

**Objectives**

- **Primary**
  - Characterize safety and tolerability of SL-701
  - Estimate percent of patients alive 12 months after initiation of SL-701
  - Estimate objective response rate (RANO & other)

- **Secondary**
  - Estimate duration of response
  - Estimate percent of patients alive and progression-free survival at 6 months after initiation of SL-701
  - Estimate distributions of progression-free survival and overall survival

- **Exploratory**
  - Estimate relationships between measures of immunologic response and anti-tumor efficacy
  - Evaluate available post-SL-701 tissue for expression status of SL-701 target antigens and infiltration of antigen-specific T cells

---

**Eligibility**

- GBM or WHO Grade IV variants
- First tumor recurrence or progression on initial multimodality treatment regimen
- HLA-A2+
- Measurable disease, tumors at least 1 cm in 2 planes (required for 80 of 100 planned subjects)
- No multi-focal tumors or tumors measuring ≥ 4 cm in any dimension
- No prior locoregional or systemic therapy (other than second resection) for recurrent/progressive GBM

---

**Study Population**

- Approx. 100 adults

**Study Centers**

- Approx. 30 sites in North America

---

Multi-center clinical trial for adults with recurrent GBM is now **open and accruing** (NCT02078648).
Every 4 weeks thereafter until disease progression

- SL-701 subcutaneous injection in the right or left upper arms with intact draining axillary nodes, alternating locations between administration dates
- 150 µg GM-CSF subcutaneous injection immediately after SL-701 administration and within 1 cm from the center of the SL-701 administration site
- 125 mg 5% imiquimod cream applied topically to the SL-701 administration site immediately and 24 hours post-SL-701 administration
Measuring immunologic responses to SL-701

Frequency of IFN-\(\gamma\)-secreting T cells that develop in response to SL-701 treatment to be measured by ELISPOT\(^{11}\)

Presence of antigen-specific CD8\(^+\) T cells that develop in response to SL-701 treatment to be assessed by tetramer analysis\(^{12}\)

\(^{11}\) Adapted from Streek, H. et al. Nat Protoc. 2009; 4 (4) ; \(^{12}\) Image from www.mobitec.com
Summary

- SL-701 is a synthetic multi-peptide immunotherapy.
- SL-701 consists of three peptides corresponding to targets overexpressed on glioma – including peptides of IL-13Rα2 and survivin engineered with amino acid substitutions to increase immunostimulatory activity.
- SL-701 has been enhanced from an earlier clinically active version by the addition of an immunogenic mutant peptide of survivin, as well as immunostimulants that may synergistically enhance cytotoxic T cell responses.
- A multi-center clinical trial with SL-701 in adults with recurrent GBM is now open and actively accruing patients (NCT02078648).