Phase 2 Trial of SL-701, a Novel Immunotherapy Targeting IL-13Rα2, EphA2, and Survivin, in Adults with Recurrent Glioblastoma (GBM)

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SL-701 Background

SL-701: 3-peptide systemic immunotherapy

Mechanism of Action

Three short synthetic peptides correspond to targets over-expressed on glioblastoma (GBM)

GBM targets: IL-13Rα2, Ephrin A2, Survivin

Designed to generate antigen specific CD8+ T cell response

CD8+ T cell response in GBM

Potential immune-related biomarker correlated with clinical outcome

1 Brain biopsy in patient with partial response (PR) after receiving SL-701: Earlier version of SL-701 used in investigator sponsored trials (IST).

**Phase 2 Trial Design (STML-701-0114)**

**Stage 1**

Eligibility: Second-line GBM

- **SL-701**
  - GM-CSF + Imiquimod
- Week: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22

**Imaging**

After week 22: SL-701 / GM-CSF / imiquimod every 4 weeks until disease progression

**Stage 2**

Eligibility: Second-line GBM

- **SL-701**
  - poly-ICLC
  - Bevacizumab
- Week: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22

**Imaging**

After week 22: SL-701 / poly-ICLC every 4 weeks and bevacizumab every 2 weeks until disease progression

*Previous investigator sponsored trials (ISTs) (~70+ patients) with earlier version of SL-701, multiple administration regimens/schedules, demonstrated tolerability with clinical activity, including major responses, in some adults and children with malignant high grade gliomas, including GBM and pediatric brainstem and non-brain stem gliomas*
Phase 2 Trial Endpoints (STML-701-0114)

• Primary
  • Stage 1 and 2: the proportion of patients alive at 12 months (OS-12)*
    • $H_0 \leq 25\%$; $H_1 > 40\%$ for both stages

• Secondary
  • Duration of response (DOR)
  • Progression-free survival at 6 months (PFS-6)
  • PFS, OS

• Exploratory
  • Correlation of immunogenicity and efficacy
  • Post-SL-701 tissue (if available) expression of glioma-associated antigen (GAA) expression status and infiltration of GAA-specific T-cells

*Primary efficacy analysis compared the lower bound of the 2-sided 95% Clopper Exact confidence interval (CI) surrounding the OS-12 rate to a value of 20%. Statistical significance to be determined if lower bound of this CI is ≥20%
Major Inclusion / Exclusion Criteria

Inclusion

• Glioblastoma or WHO Grade IV variants
• First progression after initial surgery/RT/temozolomide
• HLA A-2 positive
• Measurable disease < 4 cm
• If recurrent disease resected, eligible if no residual disease and no intermediate systemic therapy
• KPS ≥ 70%

Exclusion

• Prior bevacizumab
• Multi-focal, subependymal or leptomeningeal dissemination
• Steroid requirement of > 4mg/day of dexamethasone or equivalent
## Demographics

<table>
<thead>
<tr>
<th>demographics</th>
<th>Stage 1 (n=46)</th>
<th>Stage 2 (n=28)</th>
<th>Total (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender [n, (%)]</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (65)</td>
<td>18 (64)</td>
<td>48 (65)</td>
</tr>
<tr>
<td><strong>KPS score at screening [n, (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>29 (63)</td>
<td>13 (47)</td>
<td>42 (57)</td>
</tr>
<tr>
<td>80</td>
<td>13 (28)</td>
<td>9 (32)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>70</td>
<td>4 (8.7)</td>
<td>6 (21)</td>
<td>10 (14)</td>
</tr>
<tr>
<td><strong>Follow-up time, months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [range]</td>
<td>11 [0.7-30]</td>
<td>11 [2.0-19]</td>
<td>11 [0.7-30]</td>
</tr>
<tr>
<td><strong>Disease related genotype</strong></td>
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<td></td>
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<tr>
<td>MGMT promoter methylation status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated / Hypermethylated</td>
<td>7 (15)</td>
<td>10 (36)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>9 (20)</td>
<td>10 (36)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (65)</td>
<td>8 (29)</td>
<td>38 (51)</td>
</tr>
<tr>
<td>IDH1 mutation status:</td>
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<td></td>
<td></td>
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<tr>
<td>Mutation present</td>
<td>2 (4.3)</td>
<td>2 (7.1)</td>
<td>4 (5.4)</td>
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<tr>
<td>No mutation</td>
<td>16 (35)</td>
<td>17 (61)</td>
<td>33 (45)</td>
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<tr>
<td>Unknown</td>
<td>28 (61)</td>
<td>9 (32)</td>
<td>37 (50)</td>
</tr>
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</table>
Safety and Tolerability

Treatment Related Adverse Events (TRAEs, ≥ 5%) (n=74)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Grades n (%)</th>
<th>TRAEs n (%)</th>
<th>≥ Grade 3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TRAEs</td>
<td>All AEs</td>
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<tr>
<td>Fatigue</td>
<td>16 (22)</td>
<td>29 (39)</td>
<td>2 (2.7)²</td>
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<tr>
<td>Injection site reaction</td>
<td>13 (18)</td>
<td>15 (20)</td>
<td></td>
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<tr>
<td>Injection site erythema</td>
<td>9 (12)</td>
<td>11 (15)</td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>8 (11)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Injection site induration</td>
<td>6 (8.1)</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (8.1)</td>
<td>24 (32)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (6.8)</td>
<td>15 (20)</td>
<td></td>
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<tr>
<td>Injection site swelling</td>
<td>5 (6.8)</td>
<td>4 (8.7)</td>
<td></td>
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<tr>
<td>Skin induration</td>
<td>5 (6.8)</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>4 (5.4)</td>
<td>3 (6.5)</td>
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</tr>
</tbody>
</table>

²Both Grade 3
No Grade 4 or 5 toxicities
Overall Survival
Primary endpoint 12-month OS

Stage 1

44% (95% CI: 29-59)

Stage 2

50% (95% CI: 31-69)

Historical OS-12: ~20-38% in trials of bevacizumab in patients with recurrent GBM (BRAIN, ReACT control arm, BELOB, CABARET, and NCI’64E)\(^1\)

Above calculations by Clopper-Pearson method; NE = not estimable. \(^1\)References: BELOB: Taal et. al., Lancet Oncol 2014; BRAIN: Friedman et. al., JCO 2009; ReACT: Celldex Presentation; CARBARET: Field et. al., Neuro Oncol. 2015; NCI’64E – FDA Briefing Documents
Target-Specific CD8+ T Cell Immunophenotyping by Flow Cytometry

Frequency of antigen-specific CD8+ T cells (%)

- Immune Responders

Individual Patients
Long-Term Survivors Largely Target-Specific CD8+ T Cell Responders

Stage 2 (All patients)

Tail comprised largely of patients with target-specific T cell response

Stage 2 (Target-Specific CD8+ T cell Responders)

- 75% OS-12
- Median OS not reached
Conclusions
SL-701 + bevacizumab

- Long-term survivors: 12-month OS = 50%
- Long-term survivors comprised largely of pts with target-specific CD8+ T-cell responses
  - 12-month OS = 75%
  - Median OS not reached
- Target-specific CD8+ T-cell response = a biomarker associated with good clinical outcome
- Well-tolerated, manageable side effect profile
- Need prospective immune-related biomarkers to predict response
Acknowledgements

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