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

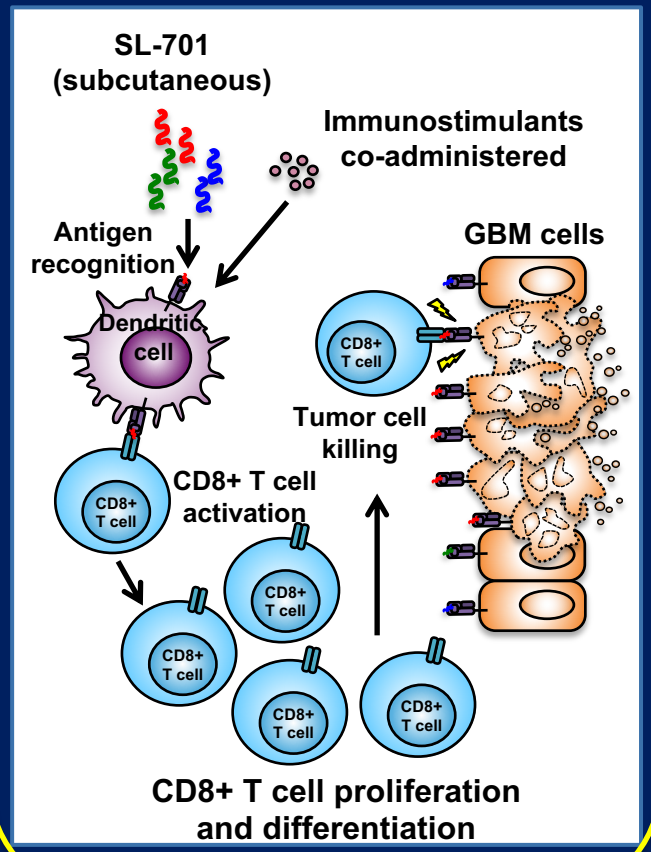
David Peereboom[1], L. Burt Nabors[3], Priya Kumthekar[4], Michael Badruddoja[9], Karen Fink[5], Frank Lieberman[11], Surasak Phuphanich[6], Erin Dunbar[8], Tobias Walbert[7], David Schiff[10], Jonathan Sherman[18], David Tran[12], Lynn Ashby[15], Nicholas Butowski[14], Fabio Iwamoto[17], Michael Schulder[13], Janice Chen[19], John Bullington[19], Shay Shemesh[19], Christopher Brooks[19], David A. Reardon[2]

[1] Cleveland Clinic Foundation, Cleveland, OH; [2] Dana-Farber Cancer Center, Boston, MA; [3] University of Alabama Cancer Center, Birmingham, AL; [4] Northwestern Brain Tumor Institute, Chicago, IL; [5] Baylor University Medical Center, Dallas, TX; [6] Cedars-Sinai Medical Center, Los Angeles, CA; [7] Henry Ford Hospital, Detroit, MI; [8] Piedmont Brain Tumor Center, Atlanta, GA; [9] Center for Neurosciences, Tucson, AZ; [10] University of Virginia, Charlottesville, VA; [11] University of Pittsburgh, Pittsburgh, PA; [12] University of Florida, Gainesville, FL; [13] North Shore University Hospital, Manhasset, NY; [14] UC San Francisco, San Francisco, CA; [15] Barrow Neurological Institute, Phoenix, AZ; [16] University of Minnesota, Minneapolis, MN; [17] Columbia University Medical Center, New York, NY; [18] George Washington University, Washington, DC; [19] Stemline Therapeutics, Inc., New York, NY

SL-701 Background

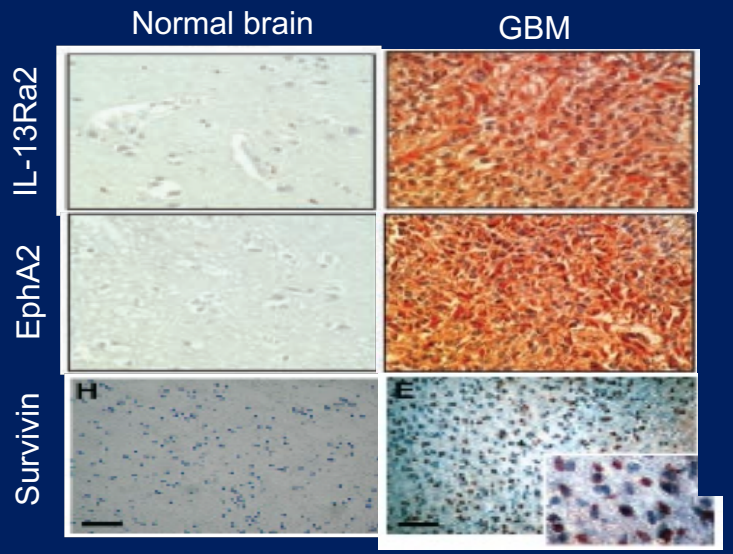
SL-701: 3-peptide systemic immunotherapy

Mechanism of Action



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

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

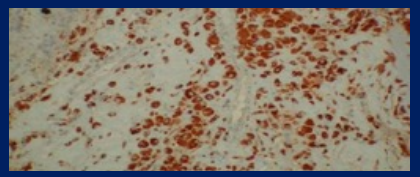


Designed to generate antigen specific CD8⁺ T cell response

CD8+ T cell response in GBM

Abundant CD8⁺ T cells

Numerous CD68⁺ macrophages



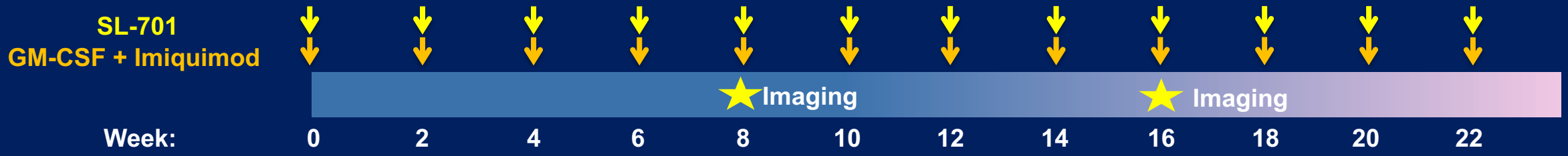
- **Potential immune-related biomarker correlated with clinical outcome**

[1]Brain biopsy in patient with partial response (PR) after receiving SL-701. Earlier version of SL-701 used in investigator sponsored trials (IST).
[2]Adapted from Uematsu, MJ. Neurooncol, 2005 and Wykosky, J. Clin Cancer Res, 2008; JCO, 2011; ASCO, 2011

Phase 2 Trial Design (STML-701-0114)

Stage 1

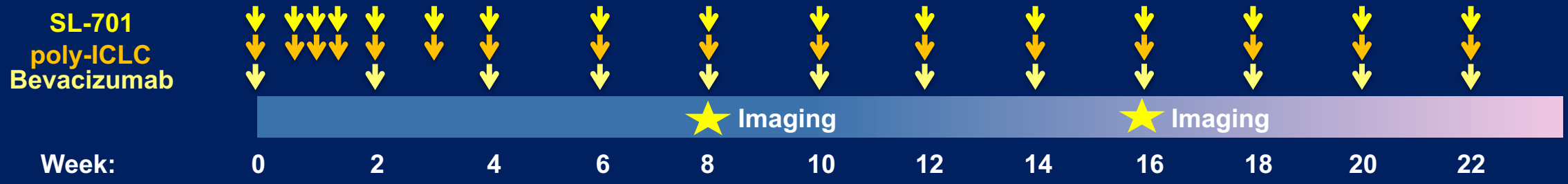
Eligibility: Second-line GBM



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

Stage 2

Eligibility: Second-line GBM



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)***
  - **$H_0 \leq 25\%$; $H_1 \geq 40\%$ 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

	Stage 1 (n=46)	Stage 2 (n=28)	Total (n=74)
Age, years			
Median [range]	54 [24-72]	60 [26-79]	57 [24-79]
Gender [n, (%)]			
Male	30 (65)	18 (64)	48 (65)
KPS score at screening [n, (%)]			
90	29 (63)	13 (47)	42 (57)
80	13 (28)	9 (32)	22 (30)
70	4 (8.7)	6 (21)	10 (14)
Follow-up time, months			
Median [range]	11 [0.7-30]	11 [2.0-19]	11 [0.7-30]
Disease related genotype			
MGMT promoter methylation status:			
Methylated / Hypermethylated	7 (15)	10 (36)	17 (23)
Unmethylated	9 (20)	10 (36)	19 (26)
Unknown	30 (65)	8 (29)	38 (51)
IDH1 mutation status:			
Mutation present	2 (4.3)	2 (7.1)	4 (5.4)
No mutation	16 (35)	17 (61)	33 (45)
Unknown	28 (61)	9 (32)	37 (50)

Safety and Tolerability

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

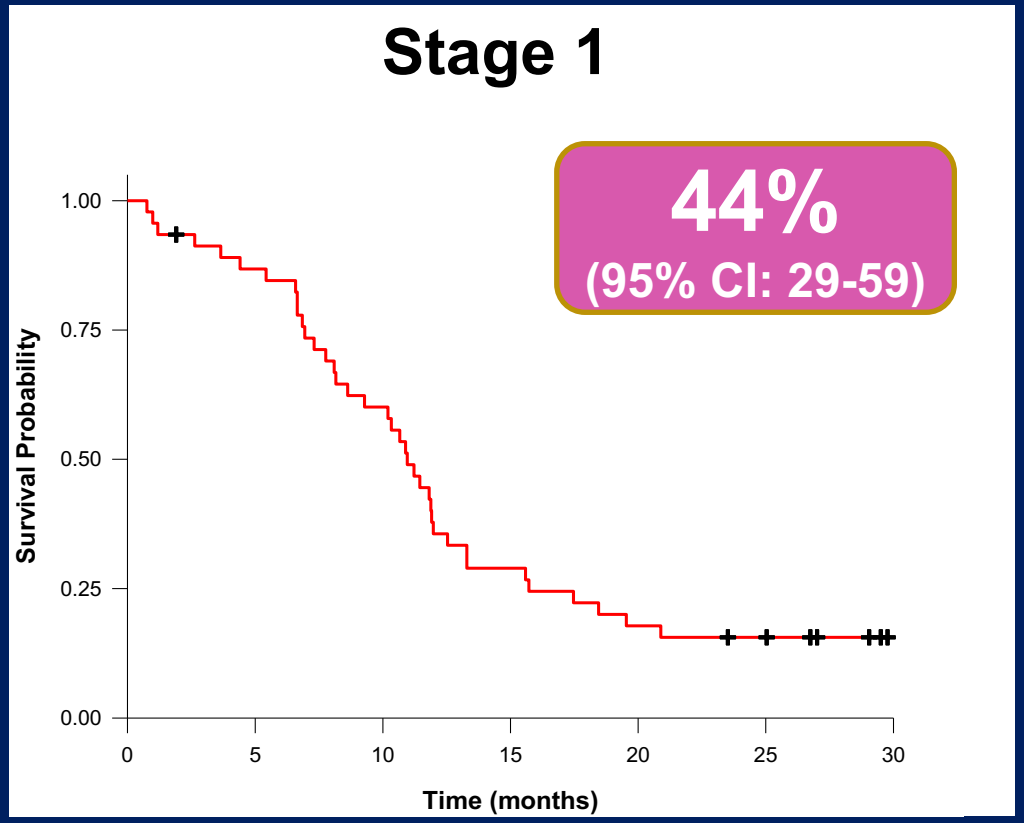
Preferred Term	All Grades n (%)		TRAEs n (%)
	TRAEs	All AEs	≥ Grade 3
Fatigue	16 (22)	29 (39)	2 (2.7)[1]
Injection site reaction	13 (18)	15 (20)	--
Injection site erythema	9 (12)	11 (15)	--
Injection site pain	8 (11)	9 (12)	--
Injection site induration	6 (8.1)	8 (17)	--
Headache	6 (8.1)	24 (32)	--
Nausea	5 (6.8)	15 (20)	--
Injection site swelling	5 (6.8)	4 (8.7)	--
Skin induration	5 (6.8)	3 (6.5)	--
Chills	4 (5.4)	3 (6.5)	--

[1]Both Grade 3
No Grade 4 or 5 toxicities

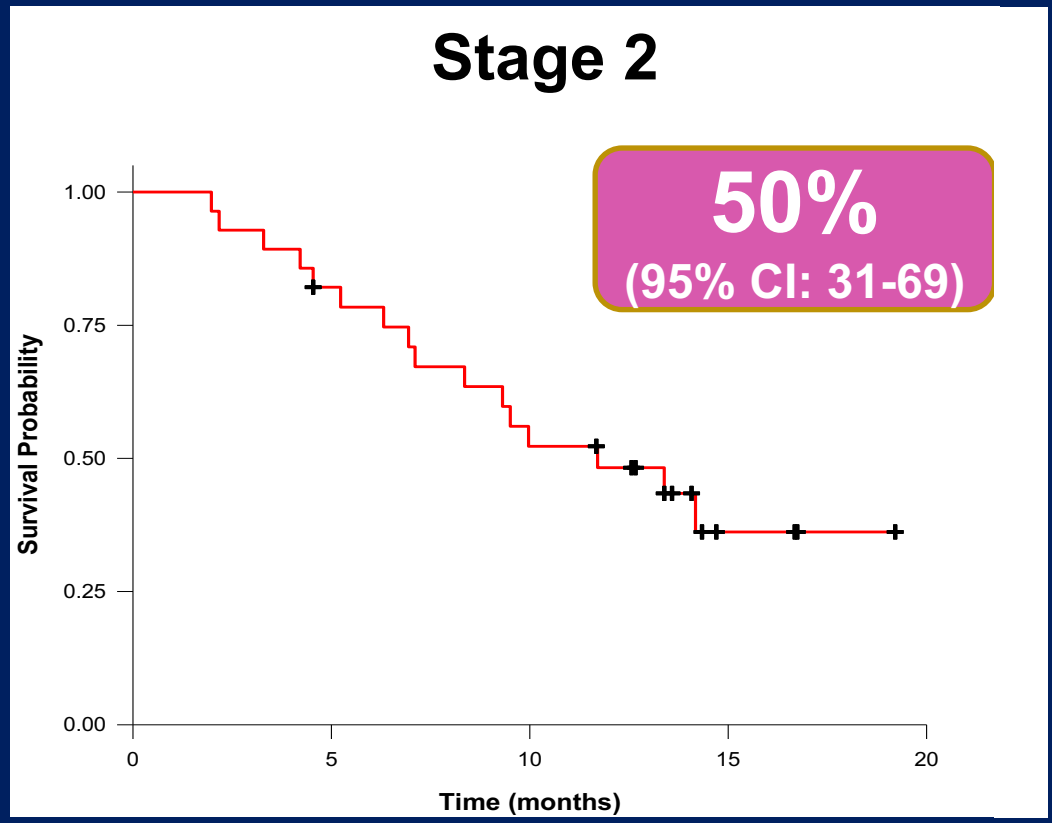
Overall Survival

Primary endpoint 12-month OS

Stage 1



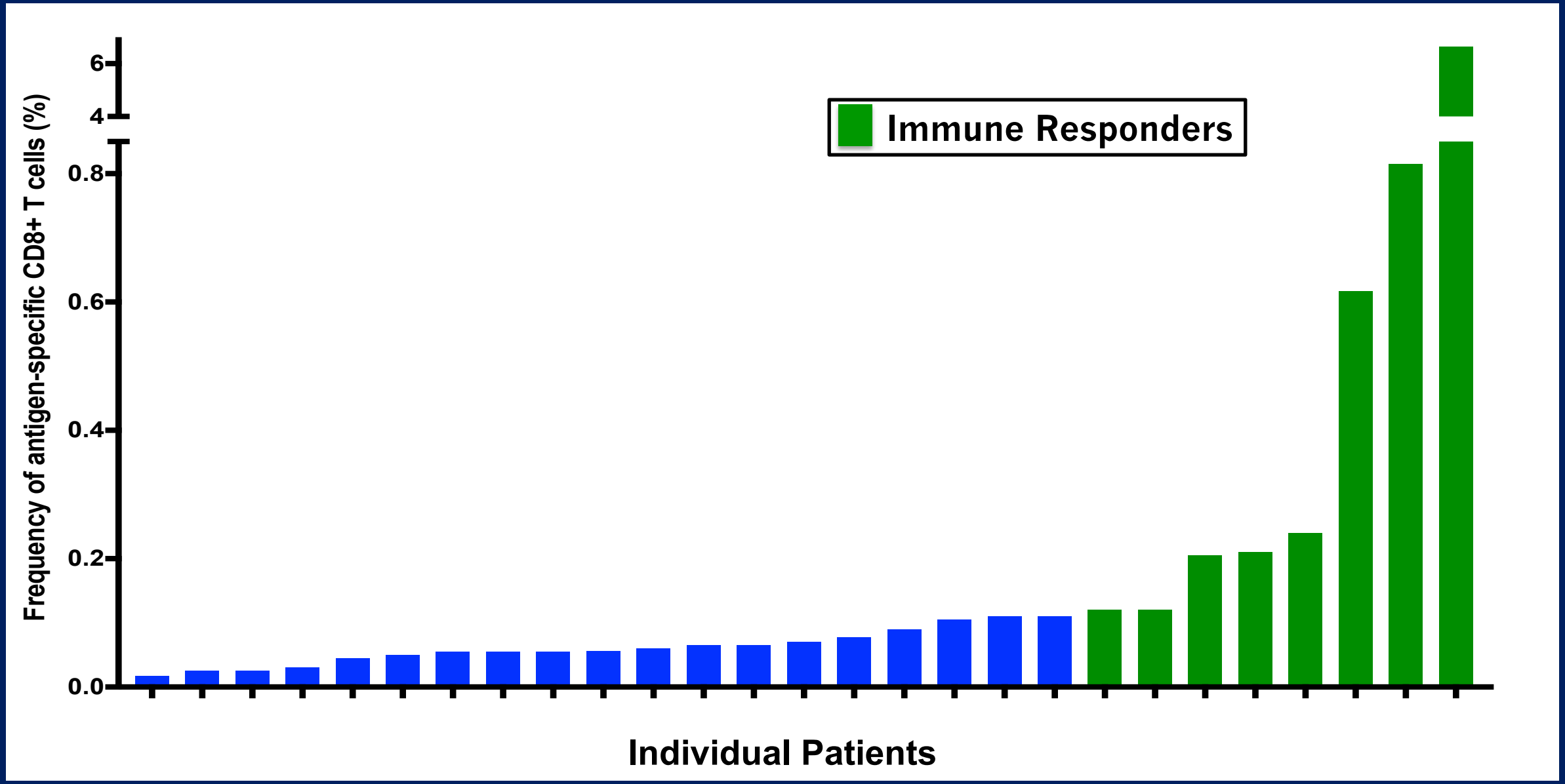
Stage 2



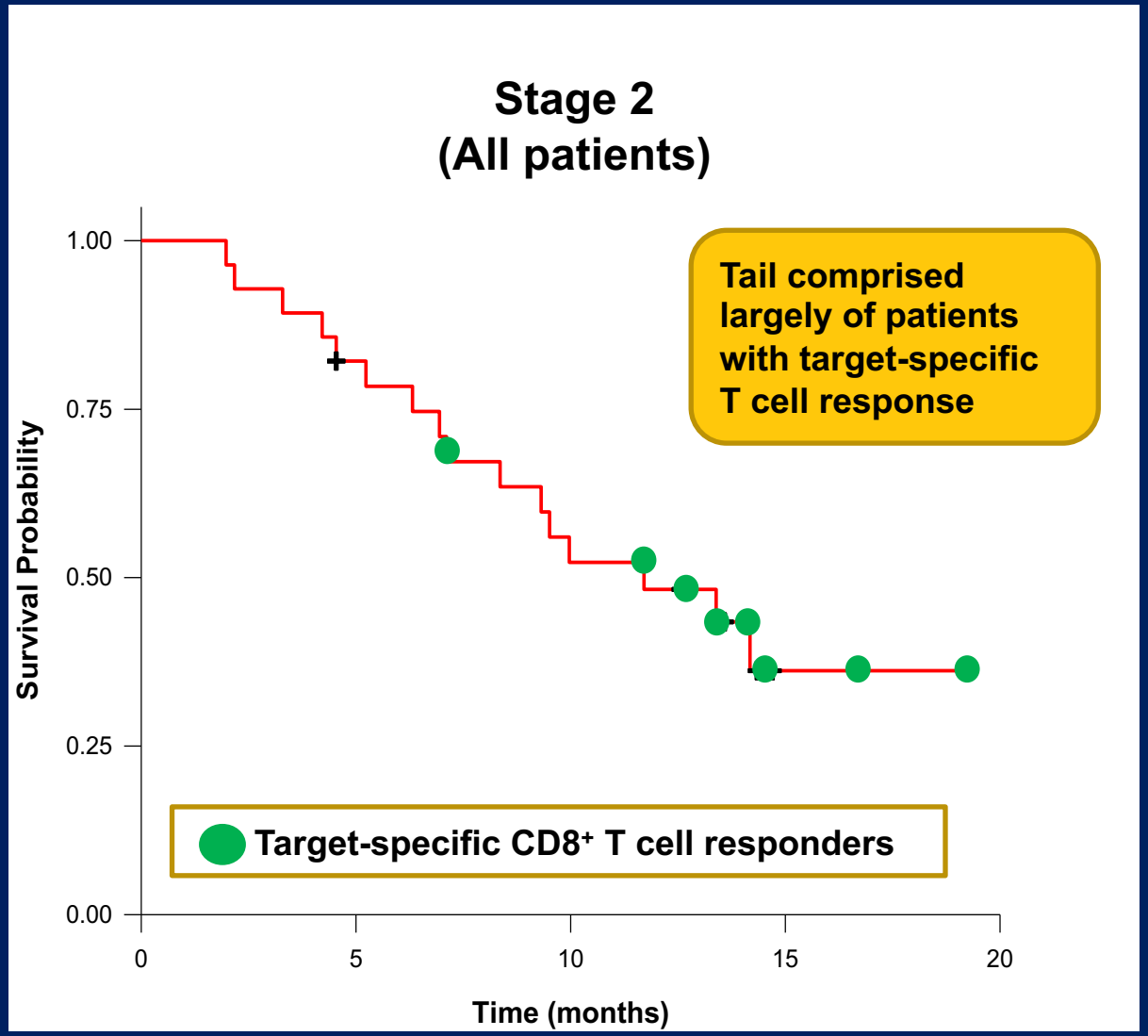
Historical OS-12: ~20-38% in trials of bevacizumab in patients with recurrent GBM (BRAIN, ReACT control arm, BELOB, CABARET, and NCI'64E)[1]

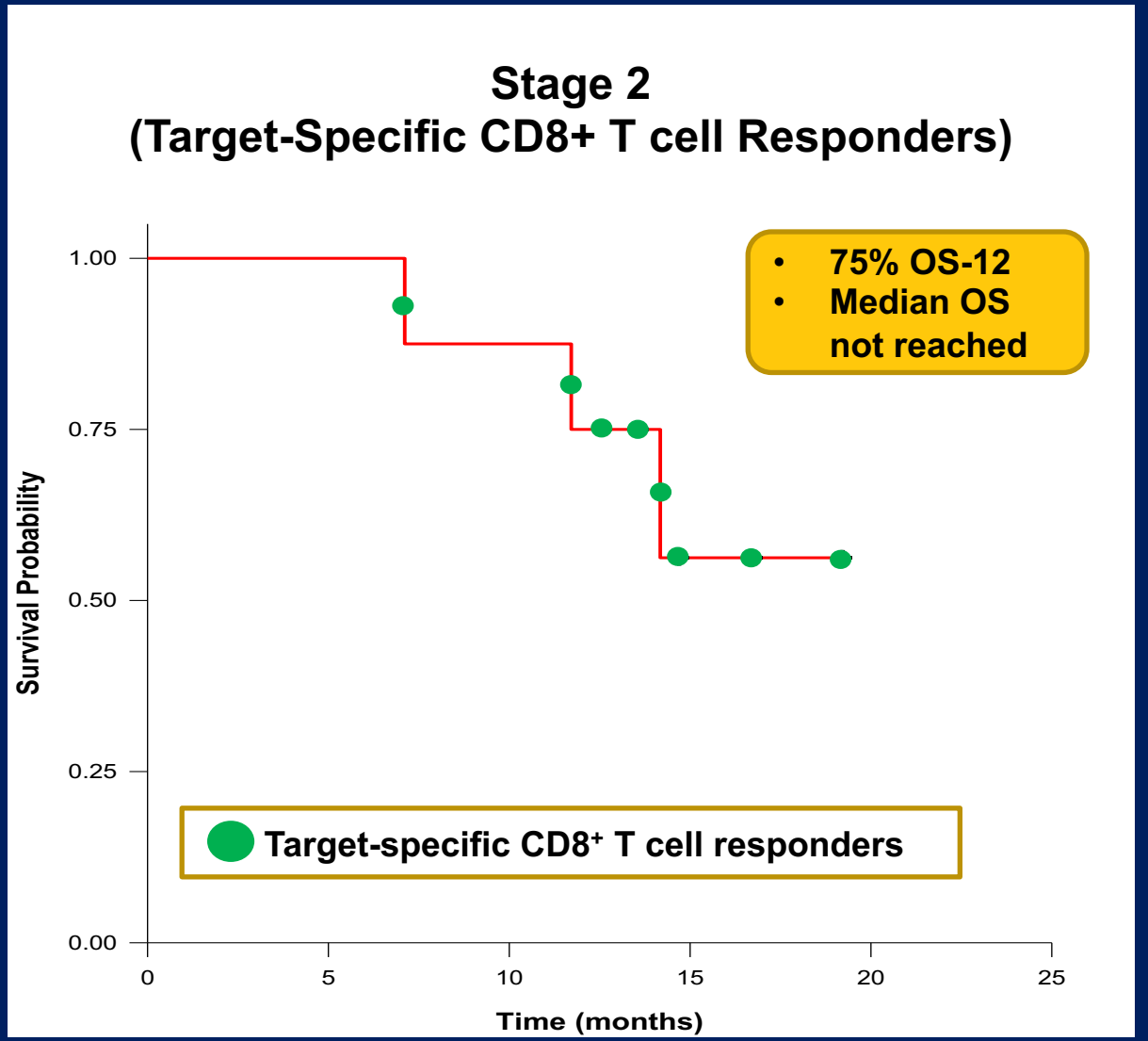
Above calculations by Clopper-Pearson method; NE = not estimable. [1]References: BELOB: *Taal et. al., Lancet Oncol 2014*; BRAIN: *Friedman et. al., JCO 2009*; ReACT: Celldex Presentation; CARBARET: *Field et. al., Neuro Oncol. 2015;* NCI'64E – FDA Briefing Documents

Target-Specific CD8+ T Cell Immunophenotyping by Flow Cytometry



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





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

We would like to thank:

- **Patients, families, investigators, and study teams at each participating center:**

- **Study sponsor: Stemline Therapeutics, Inc.**