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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Glioblastoma Background

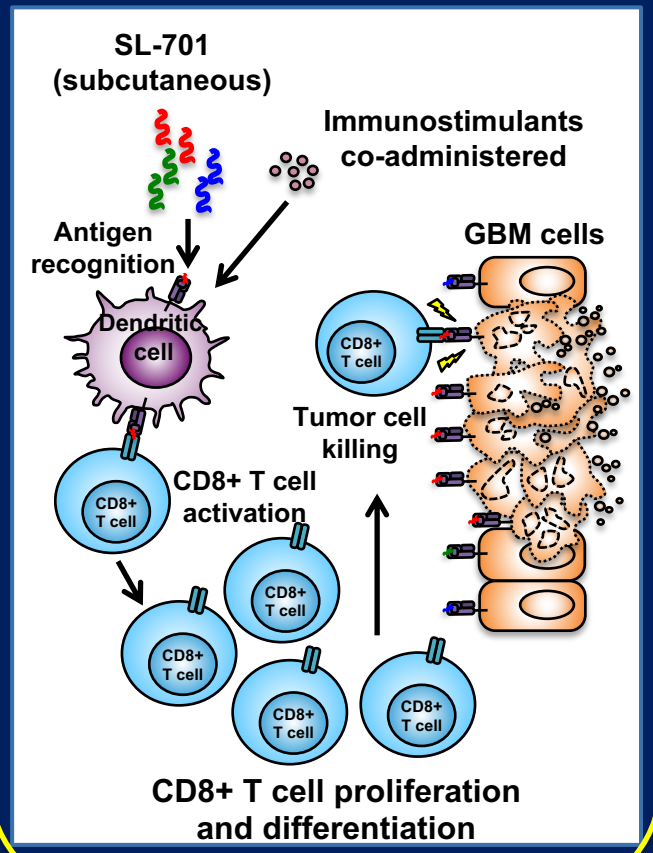
- Glioblastoma - most common primary malignant CNS tumor in adults
  - Incidence: ~22,600 in Europe and 12,800 cases in US (2018)
- Median overall survival (OS) 13-16 months for newly diagnosed patients
- Recurs in almost all patients; salvage therapies have limited efficacy
- Prognosis at recurrence
  - Median OS: ~8 months
  - PFS-6 (progression-free survival at 6 months): 10-20%

Lamborn KR, Neuro Oncol 2008;10:162-170; Gorlia T, Eur J Cancer 2012;48(8):1176-84; Wu W, Neuro Oncol 2010;12(2):164-72
Tipping M, J Clin Neurosci. 2017;44:101-106

Background and Rationale

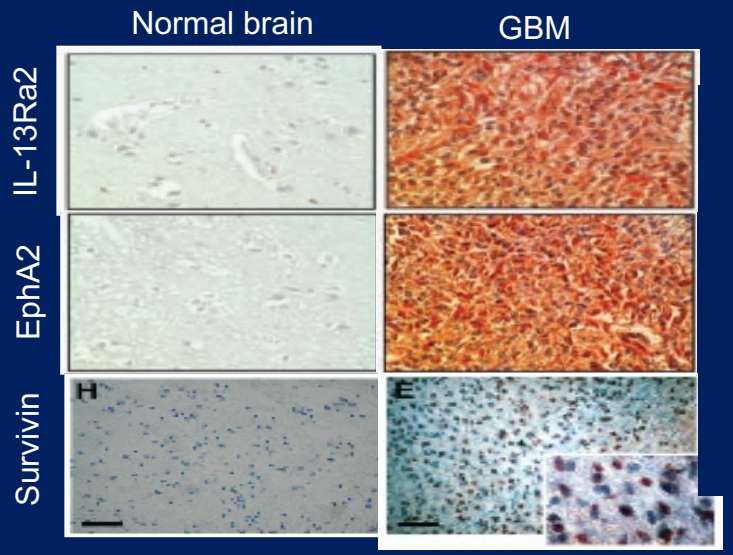
SL-701: 3-peptide systemic immunotherapy

Mechanism of Action



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

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

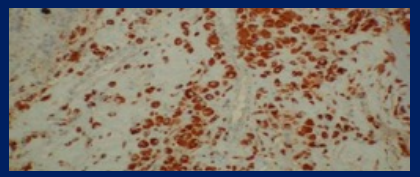


Designed to generate antigen specific CD8⁺ T cell response

CD8+ T cell response in GBM

Abundant CD8⁺ T cells

Numerous CD68⁺ macrophages



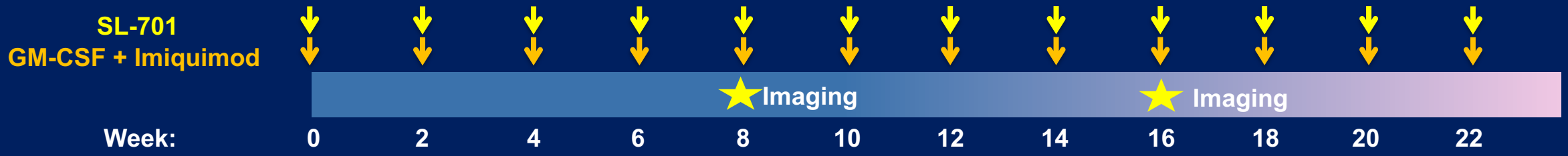
- **Potential immune-related biomarker correlated with clinical outcome**

[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

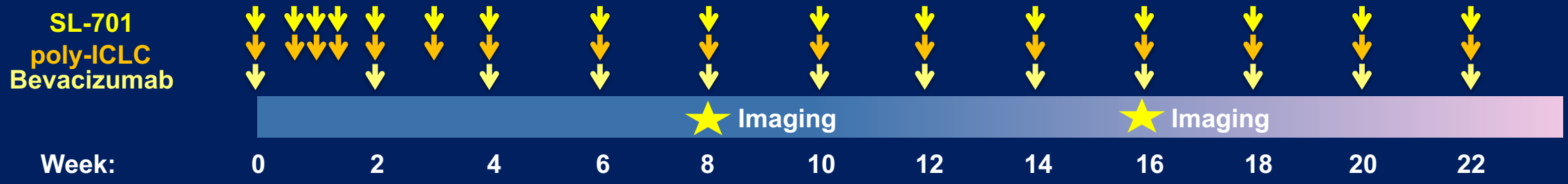
Eligibility: Second-line GBM



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)***
- **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 and Baseline Disease

	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)

	Stage 1 (n=46)	Stage 2 (n=28)	Total (n=74)
Surgery at recurrence [n, (%)]			
Complete resection	13 (28)	5 (18)	18 (24)
Partial resection	11 (24)	4 (14)	15 (20)
Prior GBM anti-cancer therapies [n, (%)]			
Temozolomide	40 (87)	26 (93)	66 (89)
Carmustine wafer	1 (2.2)	0	1 (1.4)
Investigational agent / Other	3 (6.5)	2 (7.1)	5 (6.7)
Not specified	2 (4.3)	0	2 (2.7)

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

Disease Control

Modified RANO Criteria (ITT)	Stage 1	Stage 2
n (evaluable/total)	46/46	28/28
Disease Control Rate (DCR)[1], n (rate)	10 (22%)	15 (54%)
Objective Response Rate (ORR)[2], n (rate)	1 (2%)	4 (14%)
Complete Response (CR), n (rate)	0 (0%)	2 (7%)
Partial Response (PR), n (rate)	1 (2%)	2 (7%)

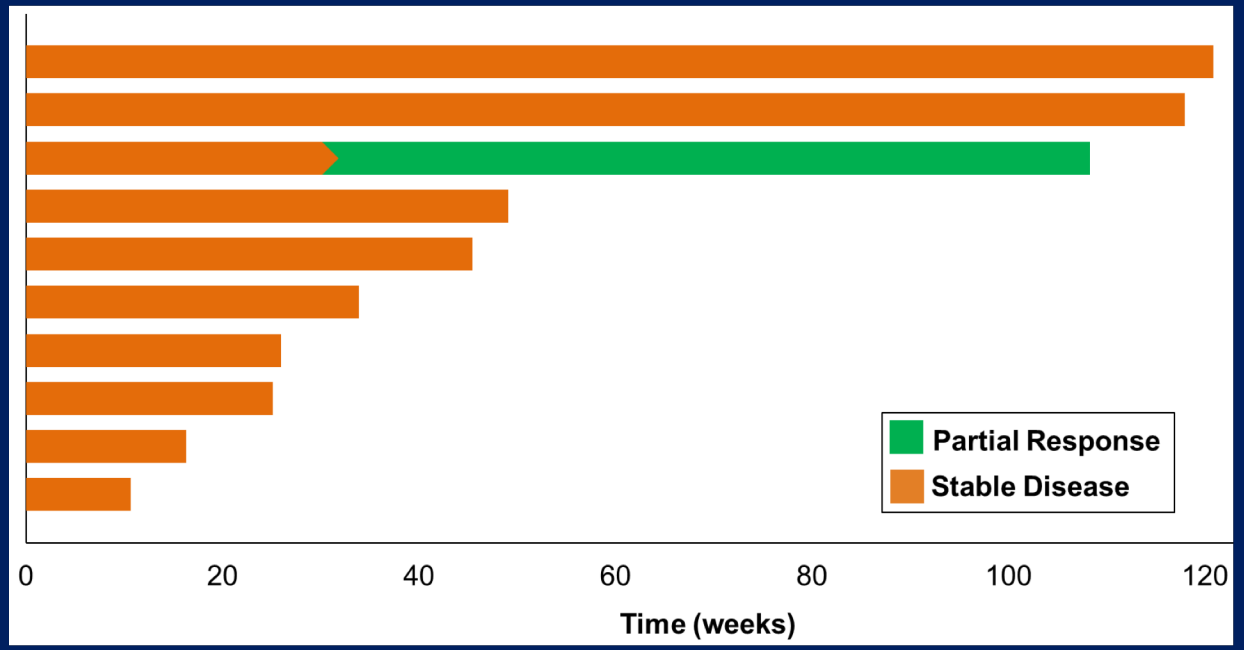
RANO = Revised Assessment in Neuro-Oncology; ITT = intent to treat; CI = confidence interval

[1]DCR is the proportion of patients who have a best response of CR, PR or SD documented on 2 consecutive MRIs ≥4 weeks apart as judged by modified RANO criteria.

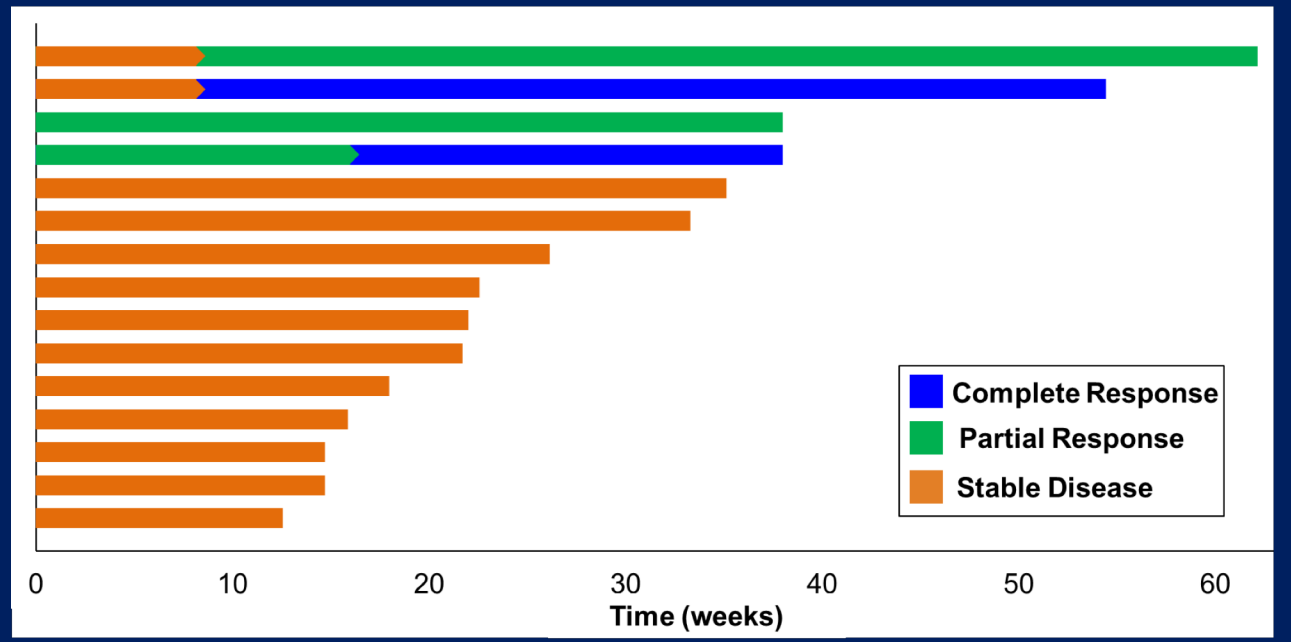
[2]ORR is the proportion of patients who have a best response of CR or PR documented on 2 consecutive MRIs ≥4 weeks apart as judged by modified RANO criteria.

Duration of Disease Control

Stage 1 (n=46)



Stage 2 (n=28)

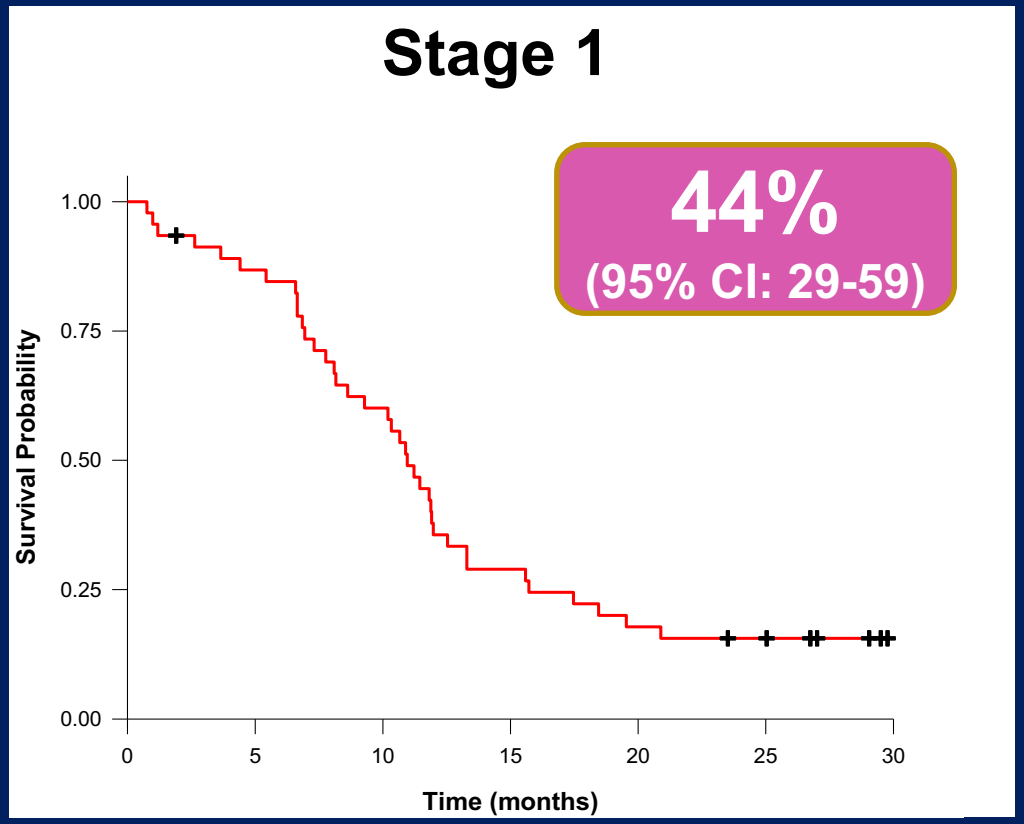


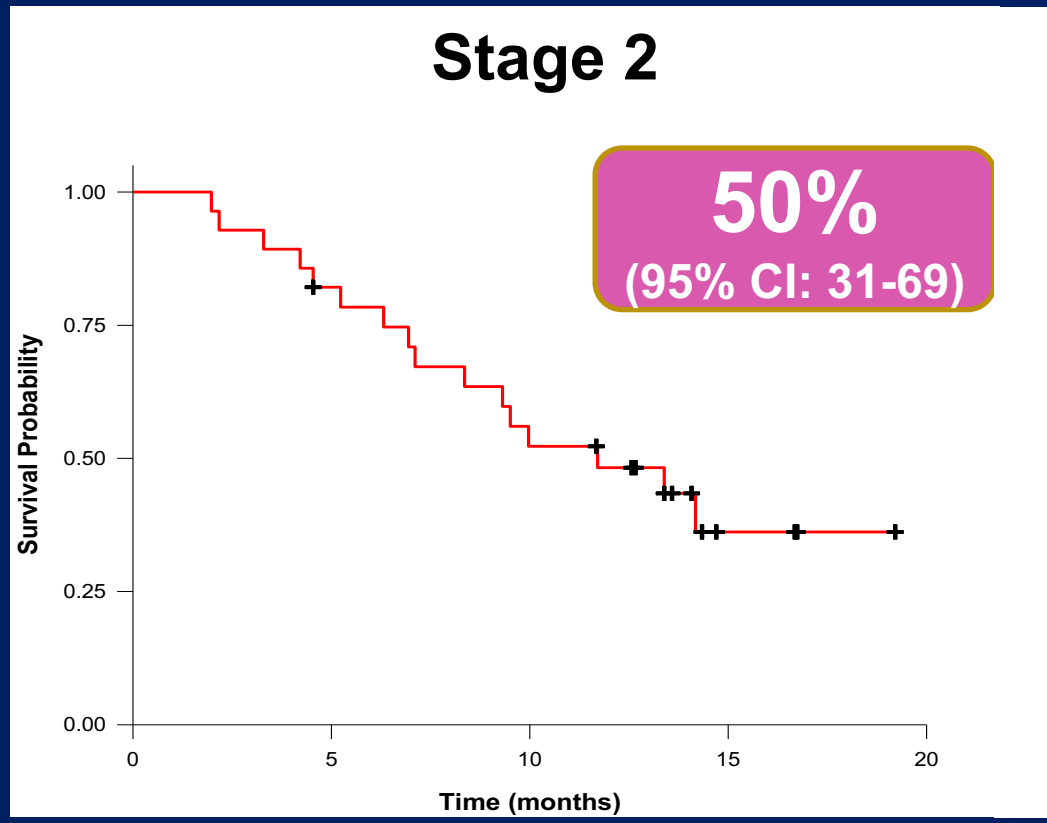
PFS-6 = 25%

Note: All responders confirmed by a second assessment according to RANO criteria

Overall Survival

Primary endpoint 12-month OS

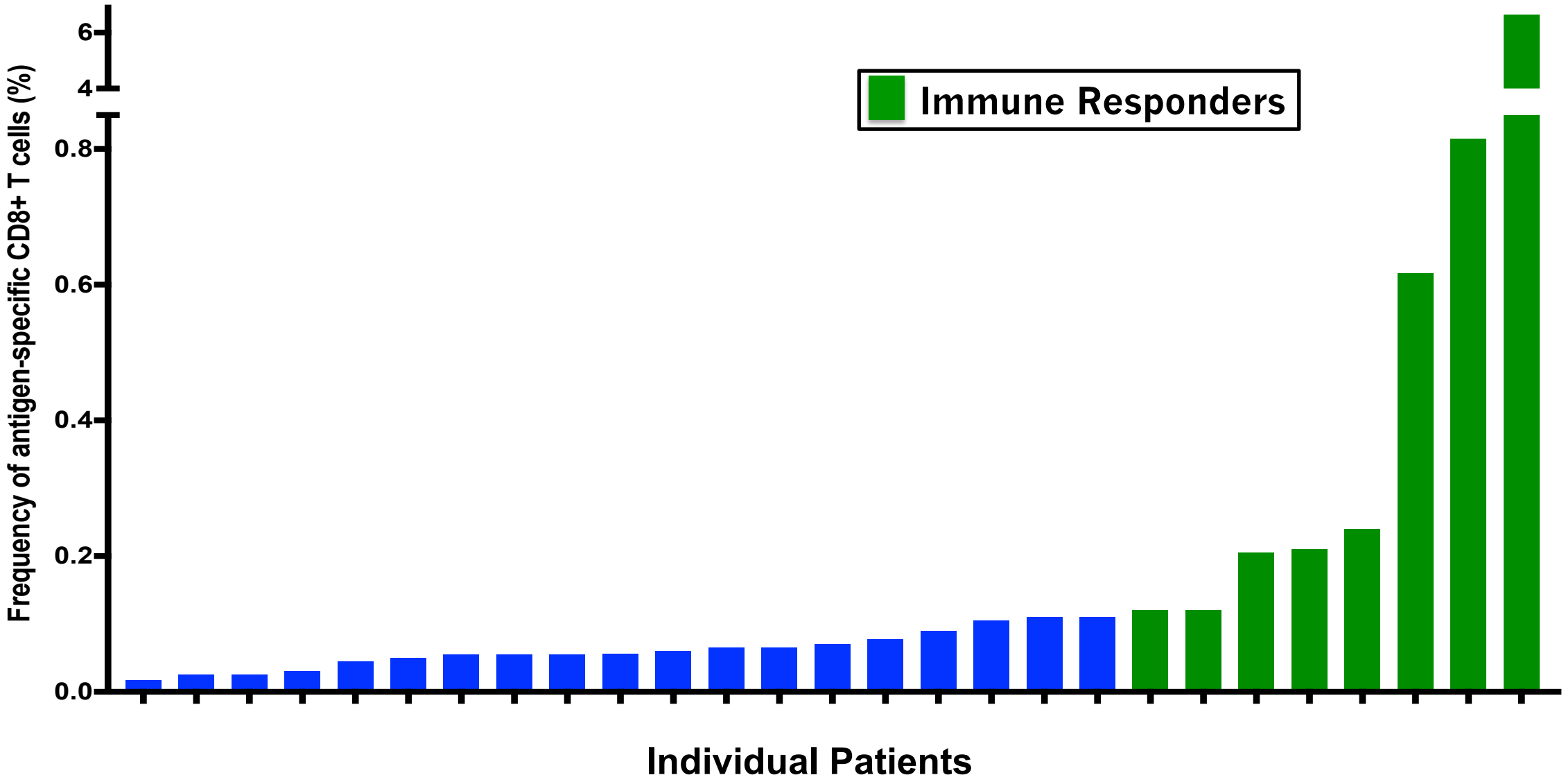




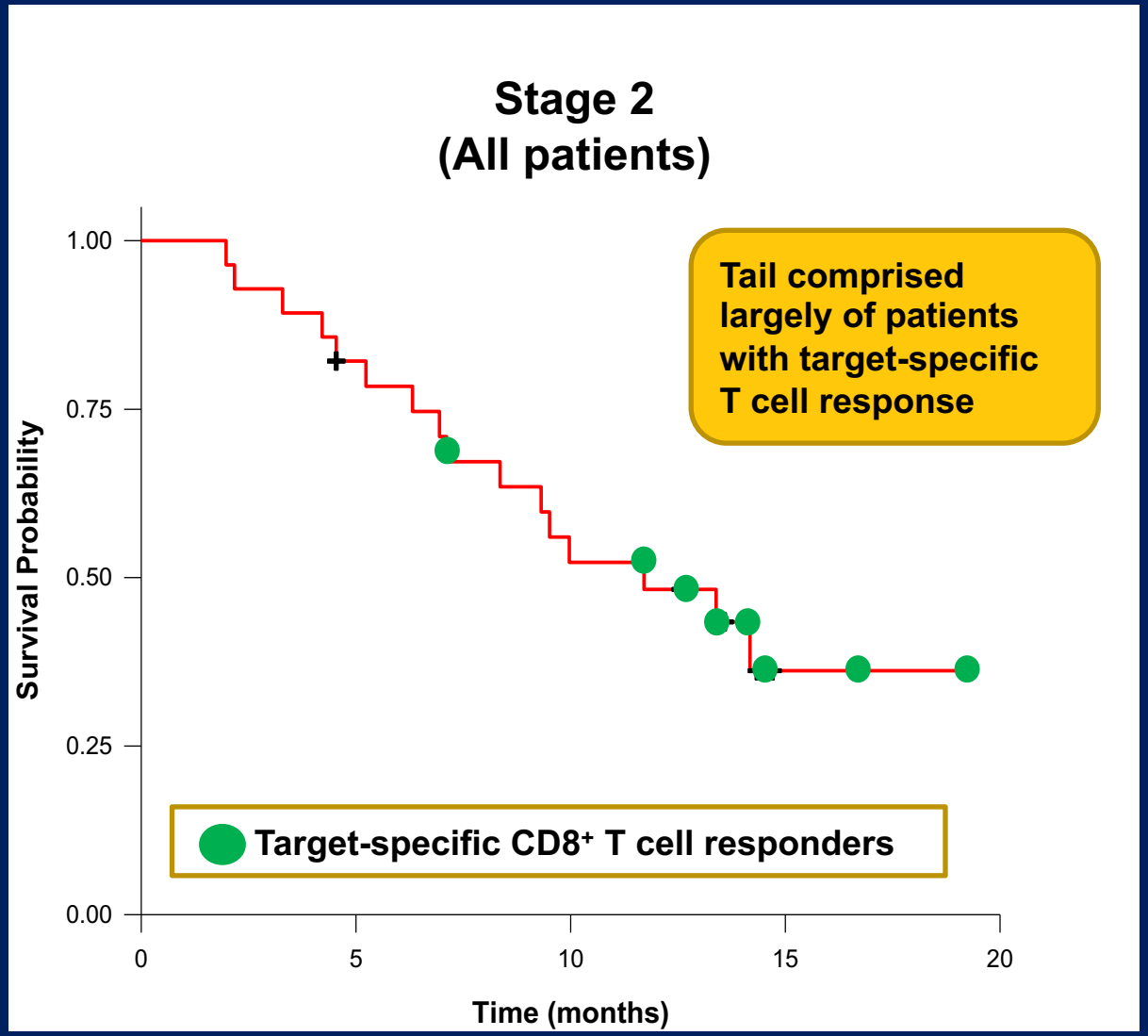
Historical OS-12: ~20-38% in trials of bevacizumab in patients with recurrent GBM (BRAIN, ReACT control arm, BELOB, CABARET, and NCI'64E)[1]

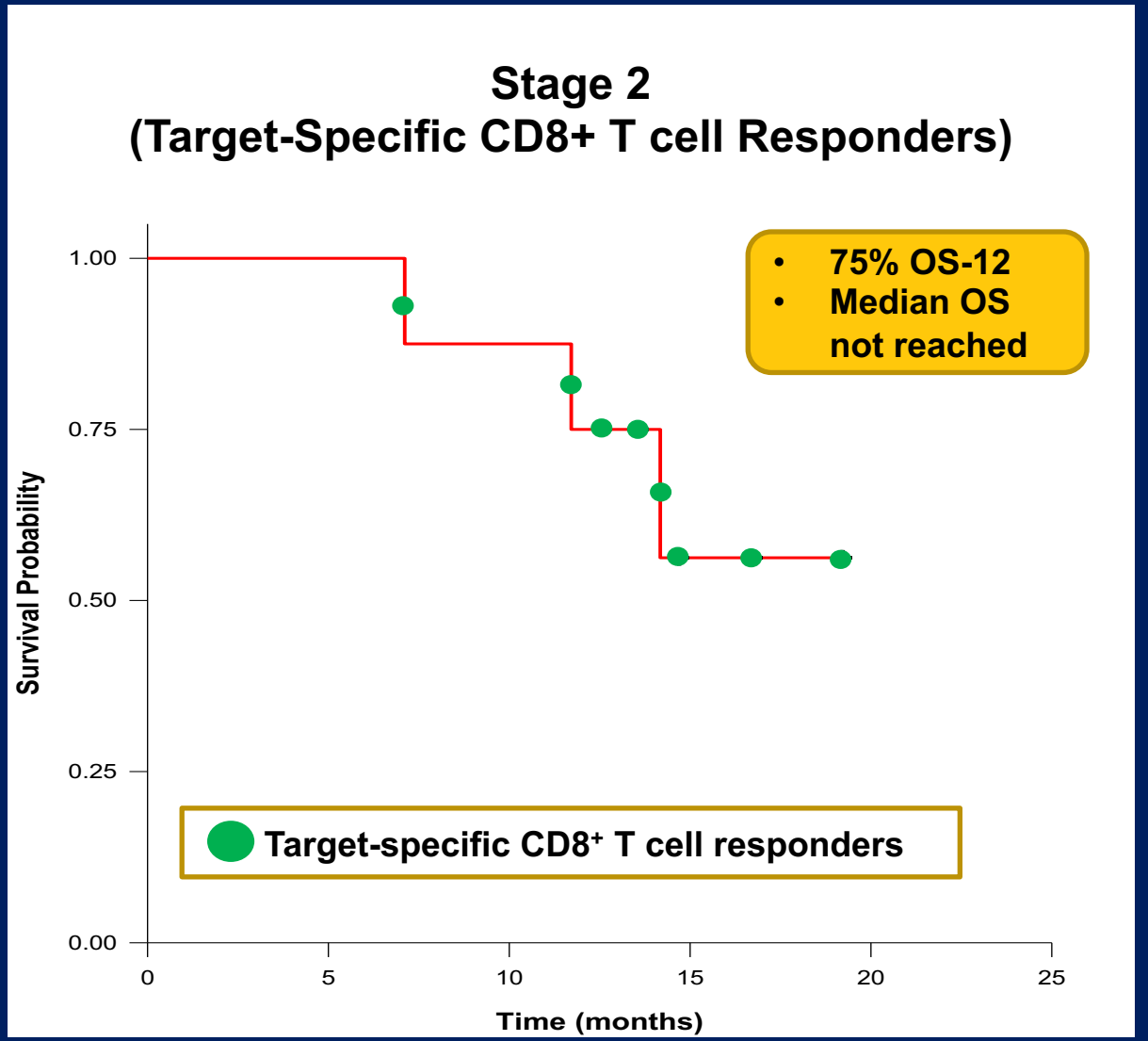
Above calculations by Clopper-Pearson method; NE = not estimable. [1]References: BELOB: *Taal et. al., Lancet Oncol 2014*; BRAIN: *Friedman et. al., JCO 2009*; ReACT: Celldex Presentation; CARBARET: *Field et. al., Neuro Oncol. 2015;* NCI'64E – FDA Briefing Documents

Target-Specific CD8+ T Cell Immunophenotyping by Flow Cytometry



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





Conclusions

- Long-term survivors: 50% 12-month OS with SL-701 + bevacizumab
- Long-term survivors comprised largely of pts with target-specific CD8+ T-cell responses
  - 12-month OS = 75%
  - Median OS not reached
  - Potential correlation of immune-related biomarker with clinical outcome
- Major responses, including CRs, and durable stable disease in second-line GBM
- Well-tolerated, manageable side effect profile
- Need prospective biomarkers to predict response
- Possible next steps including leveraging potential immune-related biomarker

Acknowledgements

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