Phase 2 trial of SL-701, a novel immunotherapy comprised of synthetic short peptides against GBM targets IL-13Rα2, EphA2, and Survivin, in adults with second-line recurrent GBM

David A. Reardon[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], Christopher Moertel[16], Michael Schulder[13], Janice Chen[19], John Bullington[19], Shay Shemesh[19], Christopher Brooks[19], Trishna Goswami[19], David Peereboom[2]

[1] Dana-Farber Cancer Center, Boston, MA; [2] Cleveland Clinic Foundation, Cleveland, OH; [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

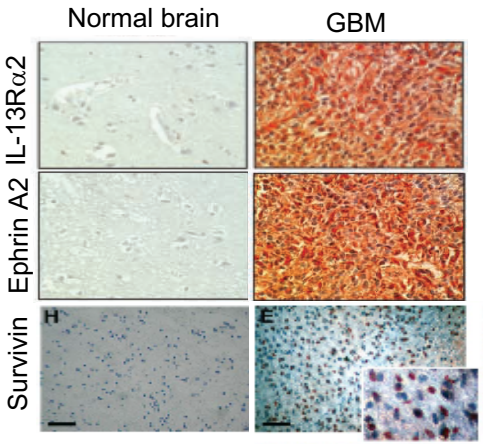
SL-701: Background

- SL-701 is an off-the-shelf, systemically-delivered (subcutaneous) immunotherapy
- Short synthetic peptides, some mutated, to generate antigen specific $CD8^+$ T cell response
  - Co-administered with immunostimulants
- Targets (IL-13Rα2, Ephrin A2, Survivin) over-expressed on glioblastoma (GBM)

GBM Targets

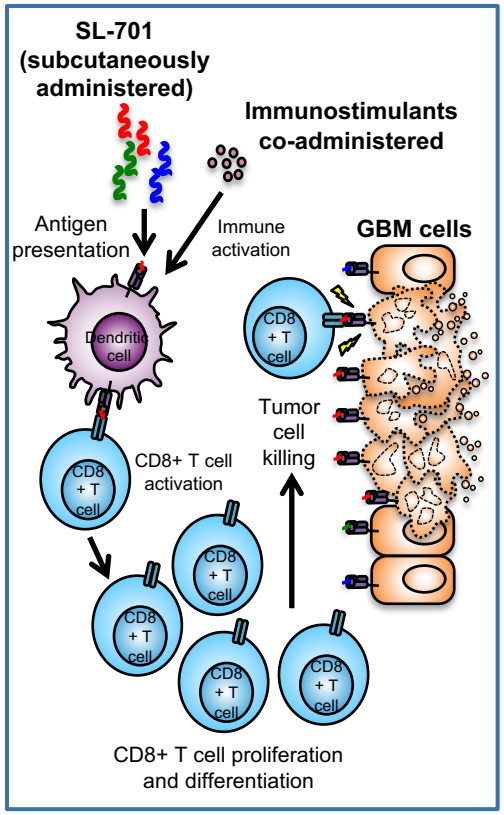
IL-13Rα2, Ephrin A2, Survivin

Overexpression of SL-701 targets on GBM



Adapted from Uematsu, MJ. Neurooncol, 2005 and Wykosky, J. Clin Cancer Res, 2008

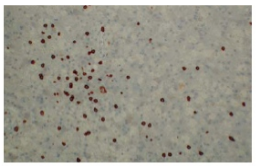
Mechanism of Action

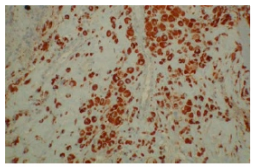


SL-701 Directs $CD8^+$ T cells to GBM

T cell response/inflammation in brain biopsy post-SL-701 (earlier version)

Abundant $CD8^+$ T cells





Numerous $CD68^+$ macrophages

From: JCO, 2011; ASCO, 2011

SL-701: Clinical Trials Summary

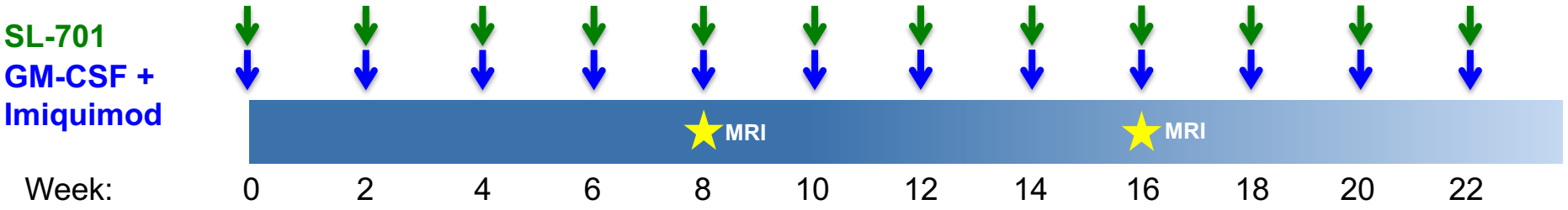
- **Phase 2 trial**
  - Stage 1 (Single agent): SL-701 + immunostimulants (GM-CSF + Imiquimod)
  - Stage 2 (Combination): SL-701 + immunostimulant (poly-ICLC) + bevacizumab
  - Major objective responses and durable stable diseases in both Stages, including complete responses (CRs) in Stage 2
  - Long-term survivors in both Stages, including ~48% 12-month overall survival probability in Stage 2
  - Robust target-specific $CD8^+$ T cell responses seen in patients with clinical benefit

[1]*JCO, 2011; ASCO, 2011 Poster#2506; AACR, 2012 Poster#LB-135*

SL-701: Phase 2 Trial Design (STML-701-0114)

Stage 1

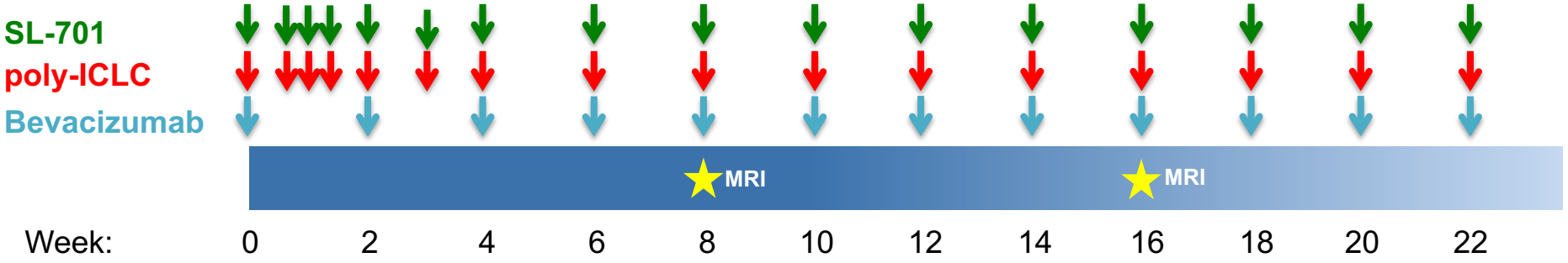
Eligibility: Second-line GBM



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

Stage 2

Eligibility: Second-line GBM



After week 22: SL-701 / poly-ICLC every 4 weeks and bevacizumab (as per label) every 2 weeks thereafter until disease progression

SL-701: Eligibility Criteria

Select inclusion criteria

- ≥18 years old with GBM or WHO Grade IV variants with KPS score ≥70%
- Unequivocal evidence of progression after initial treatment with surgery/xrt/TMZ by appropriate imaging
- Patients with no prior resection must have measurable disease; those with prior resection for recurrence are eligible if no residual disease and no intermediate systemic therapy
- No chemotherapy or investigational agents within 3 weeks prior to start of SL-701
- HLA A-2 positive
- Adequate baseline organ function:
  - Serum creatinine ≤1.5 ULN
  - AST and ALT ≤2.5 times the upper limit of normal (ULN)
  - Bilirubin ≤1.5 ULN
  - ANC ≥1000/μL, platelets≥100,000/μL

Select exclusion criteria

- Persistent clinically significant toxicities G≥2 from previous chemotherapy
- Prior bevacizumab or prior therapy for recurrent/progressive GBM
- Contrast enhancing tumor that is multi-focal, associated with subependymal or leptomeningeal dissemination or ≥4cm in size
- Requirement of > 4mg/day of dexamethasone or equivalent or need for increasing steroids dose within 7 days prior to start of treatment
- <4 weeks since surgical resection or<7 days since stereotactic biopsy
- Need for anti-coagulation or existing coagulopathy or active bleeding
- Known immunosuppressive disease or HIV, Hep B or C infection

SL-701: 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 (65.2)	18 (64.3)	48 (64.9)
KPS score at screening [n, (%)]			
100	6 (13.0)	5 (17.9)	11 (14.9)
90	23 (50.0)	8 (28.6)	31 (41.9)
80	13 (28.3)	9 (32.1)	22 (29.7)
70	4 (8.7)	6 (21.4)	10 (13.5)
Follow-up time, months			
Median [range]	10.9 [0.7-29.7]	10.8 [2.0-19.2]	10.9 [0.7-29.7]
Disease related genotype			
MGMT promoter methylation status:			
Methylated / Hypermethylated	7 (15.2)	10 (35.7)	17 (23.0)
Unmethylated	9 (19.6)	10 (35.7)	19 (25.7)
Unknown	30 (65.2)	8 (28.6)	38 (51.3)
IDH1 mutation status:			
Mutation present	2 (4.3)	2 (7.1)	4 (5.4)
No mutation	16 (34.8)	17 (60.7)	33 (44.6)
Unknown	28 (60.9)	9 (32.1)	37 (50.0)

	Stage 1 (n=46)	Stage 2 (n=28)	Total (n=74)
Surgery at recurrence [n, (%)]			
Complete resection	26 (56.5)	20 (71.4)	46 (62.2)
Partial resection	16 (34.8)	7 (25.0)	23 (31.1)
No surgery at recurrence	4 (8.7)	1 (3.6)	5 (6.7)
Prior GBM anti-cancer therapies [n, (%)]			
TMZ based therapy	40 (86.9)	26 (92.9)	66 (89.2)
Gliadel 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)

SL-701: Treatment Related Adverse Events (≥ 5%) (n=74)

Preferred Term	All Grades n (%)		TRAEs n (%)
	TRAEs	All AEs	≥ Grade 3
Fatigue	16 (21.6)	29 (39.2)	2 (2.7)[1]
Injection site reaction	13 (17.6)	15 (20.3)	--
Injection site erythema	9 (12.2)	11 (14.9)	--
Injection site pain	8 (10.8)	9 (12.2)	--
Injection site induration	6 (8.1)	8 (17.4)	--
Headache	6 (8.1)	24 (32.4)	--
Nausea	5 (6.8)	15 (20.3)	--
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 cases were Grade 3

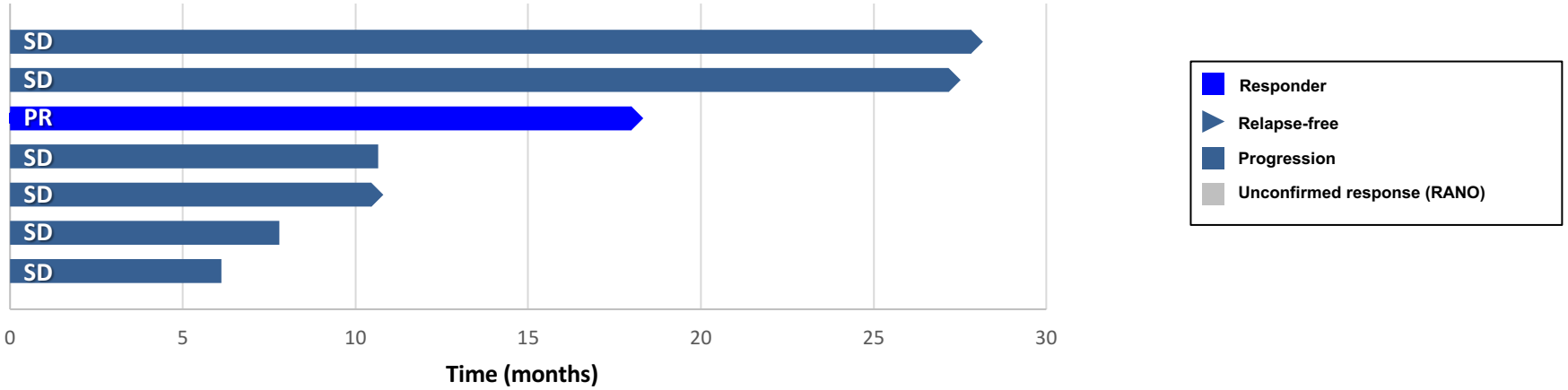
SL-701: Disease Control, Including Major Responses

	Stage 1	Stage 2
n (evaluable/total)	46/46	28/28
Disease control[1], n (rate; DCR)	16 (35%)	27 (96%)
Overall response, n (rate; ORR)	1 (2%)	6 (21%)
Complete response (CR), n (rate)	0 (0%)	2 (7%)
Partial Response (PR), n (rate)	1 (2%)	4 (14%)
Stable Disease (SD), n (rate)	15 (33%)	21 (75%)

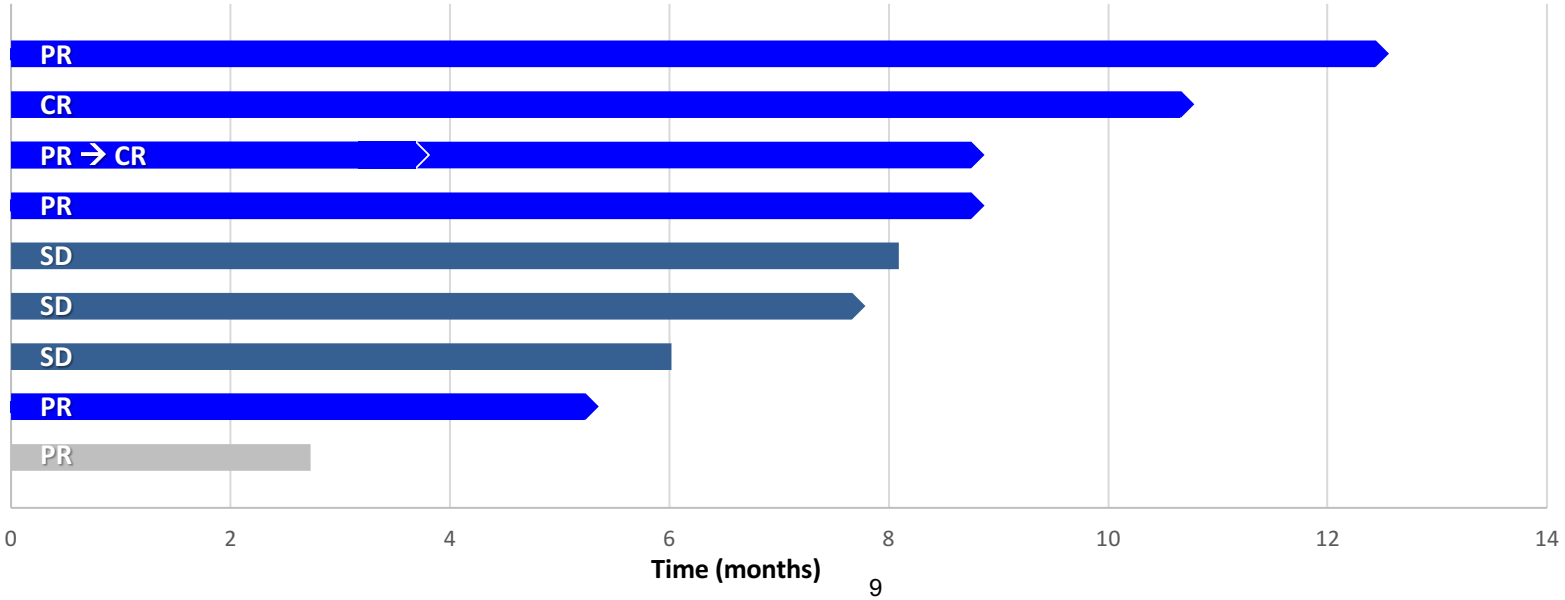
[1]Disease control = CR + PR + SD

SL-701: Duration of Disease Control

Stage 1 (n=46): Duration of Response or ≥6 month Stable Disease: 6.1 – 27.8 months

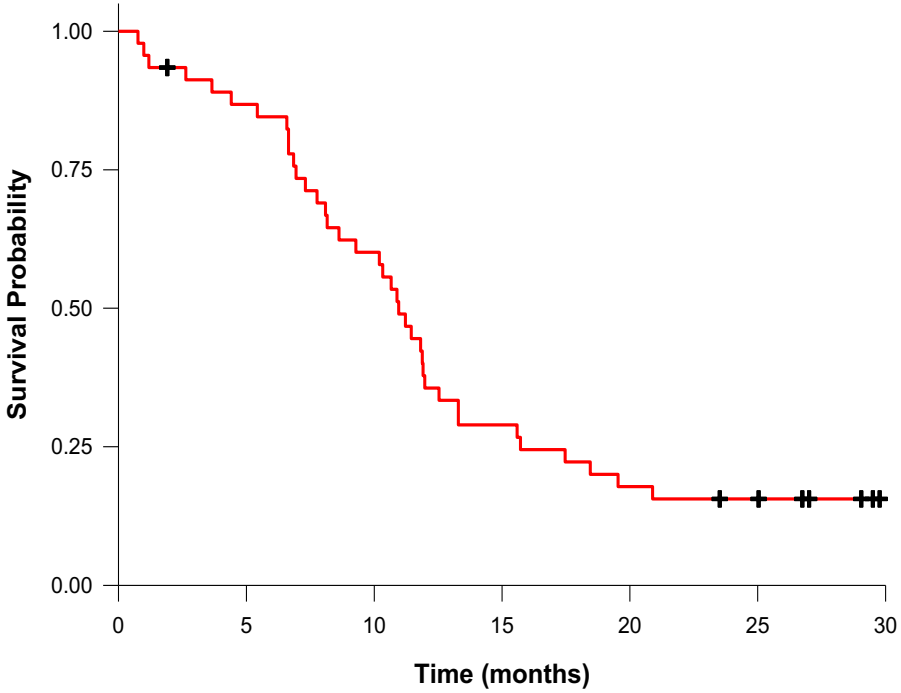


Stage 2 (n=28): Duration of Response or ≥6 month Stable Disease: 2.7 – 12.4 months



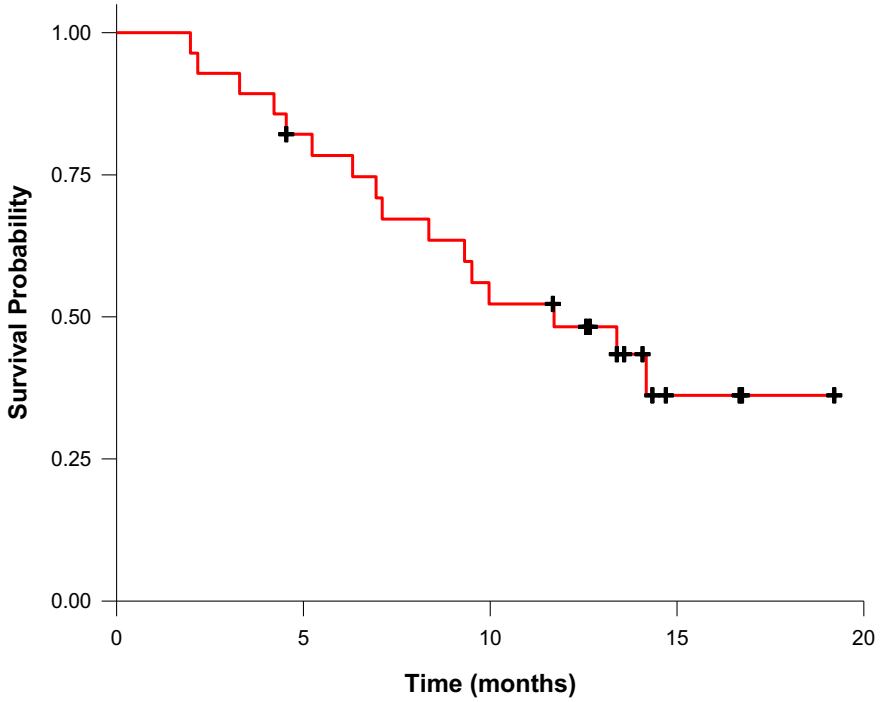
SL-701: Overall Survival (OS)

Stage 1, n=46



OS-12: 36%
Median OS = 10.9 months

Stage 2, n=28

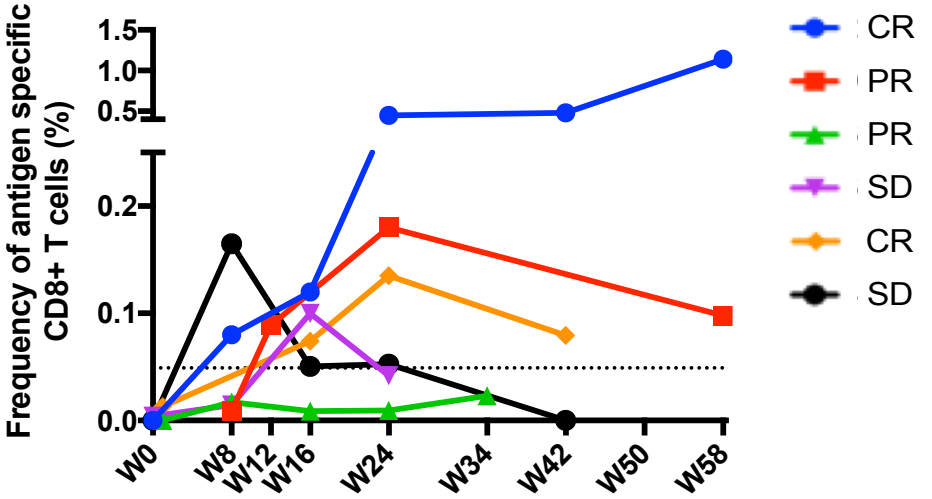


OS-12: 48%
Median OS = 11.7 months

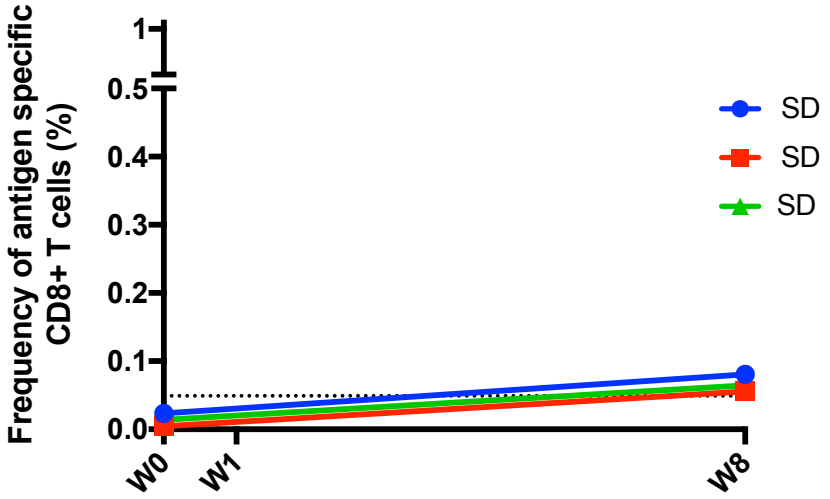
OS-12 = Overall Survival at 12 months

SL-701: Immune Response Tracks Clinical Benefit

Stage 2 patients with CR, PR, or SD (≥6 months)



Stage 2 patients with SD (<6 months)



Purpose

- Assess relative immune responses by flow cytometry in patients experiencing clinical benefit

Methods

- Patient subsets selected for immune analysis based on
  - CR, PR, or SD (≥6 months) versus SD <6 months
- PBMCs analyzed from 9/28 (32%) of Stage 2 patients
  - Cells stimulated for 24 hours with pool of all 3 peptides
  - Media (negative control)
  - PMA/Ionomycin (positive control)

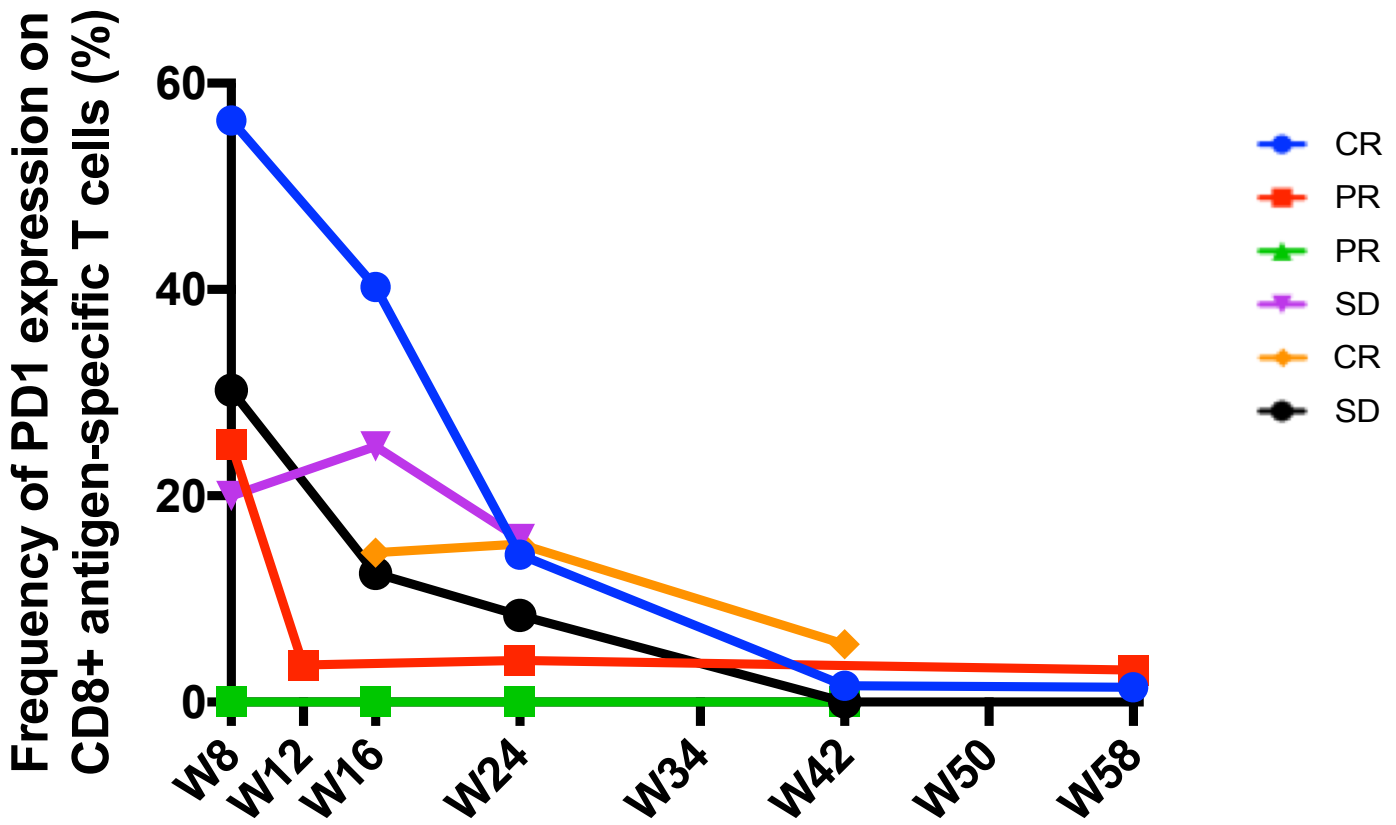
Staining Panel

- CD8+ IFNɣ+ antigen-specific T cells are graphed as frequency of CD8+ population
- Markers tested: INFɣ, TNF-α, IL-2, CCR7 (CD197), PD-1 (CD279), CD8, CD3, CD45RA

Cut Off for Positivity

- Dotted line = mean of untreated + 3*Standard Deviations

SL-701: PD-1 Expression on Target-Specific CD8+ T cells from Patients Experiencing Clinical Benefit

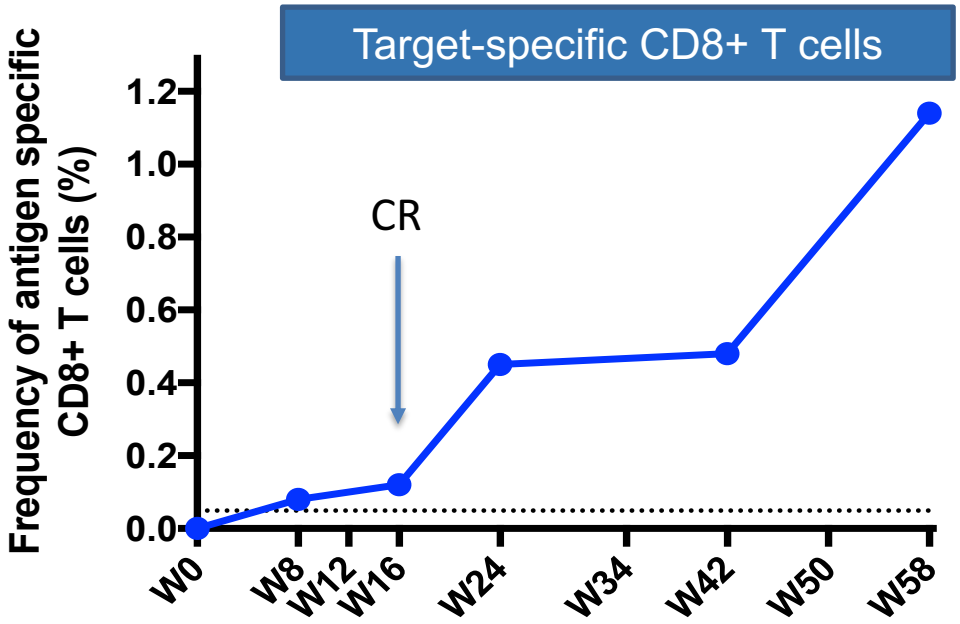


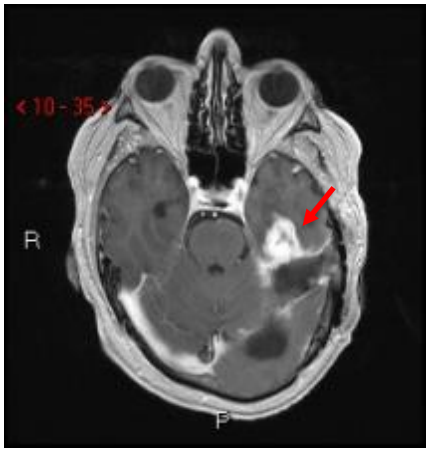
- Patient derived antigen specific CD8+ T cells were analyzed for PD-1 expression by flow cytometry at various time points
- Provides a potential rationale for combining SL-701 with anti-PD-1 or other checkpoint inhibitors

SL-701: Clinical Benefit and Robust Immune Response

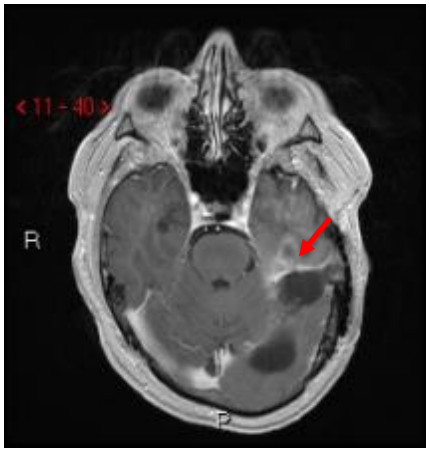
Patient Narrative

- 60 year-old male
- Grade IV GBM, KPS 90%, MGMT promoter methylated, non-mutated IDH1
- Prior treatment:
  - 1 resections + Stupp + Veliparib
- Received SL-701 + bevacizumab
  - CR after 4 months
  - Confirmed by 2nd assessment

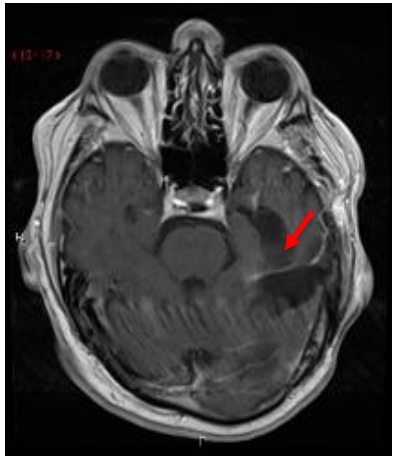




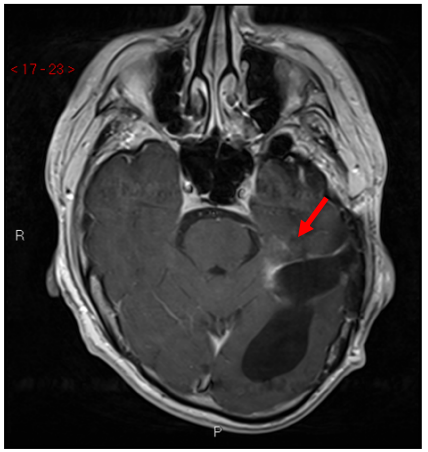
Pre-SL-701



2 months of SL-701



9 months of SL-701

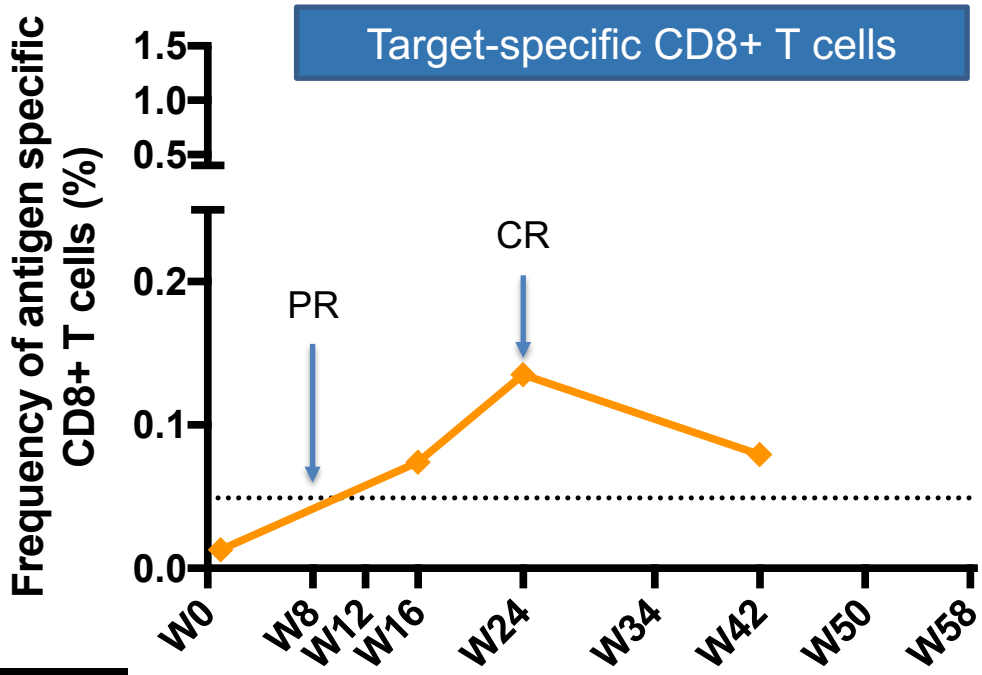


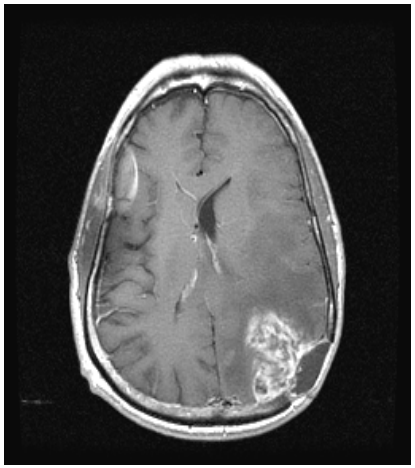
11 months of SL-701

SL-701: Clinical Benefit and Robust Immune Response

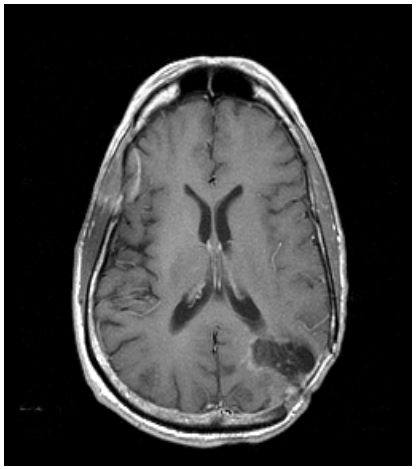
Patient Narrative

- 51 year-old male
- Grade IV GBM, KPS 90%, MGMT promoter methylated
- Prior treatment:
  - 2 resections + Stupp
- Received SL-701 + bevacizumab
  - PR after 2 months, confirmed by 2nd assessment
  - Subsequently converted to CR, confirmed by 2nd assessment





Pre-SL-701



6 months of SL-701

SL-701: Conclusions and Next Steps

- Major responses and durable stable diseases with SL-701 alone and in combination with bevacizumab in second-line GBM
- Well-tolerated, very manageable side effect profile
- Long-term survivors with SL-701 alone (Stage 1) and in combination with bevacizumab (Stage 2), including ~48% 12-month OS survival probability in Stage 2
- Robust target-specific $CD8^+$ T-cell responses in patients experiencing clinical benefit consistent with mechanism of action
- Given the major unmet medical need in GBM and promising safety and efficacy data generated to date with SL-701, Stemline is considering next steps including possible registration-directed trial designs

Acknowledgements

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  - Piedmont Brain Tumor Center
  - Center for Neurosciences
  - University of Virginia
  - University of Pittsburgh
  - University of Florida
  - North Shore University Hospital
  - UC San Francisco
  - Barrow Neurological Institute
  - University of Minnesota
  - Columbia University Medical Center
  - George Washington University
- This study is sponsored by Stemline Therapeutics, Inc.

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