Personalized, off-the-shelf KRAS neoantigen-specific immunotherapy for the treatment of advanced solid tumors: Clinical benefit associated with decreases in ctDNA (SLATE-KRAS)

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DECLARATION OF INTERESTS

Chrisann Kyi, MD

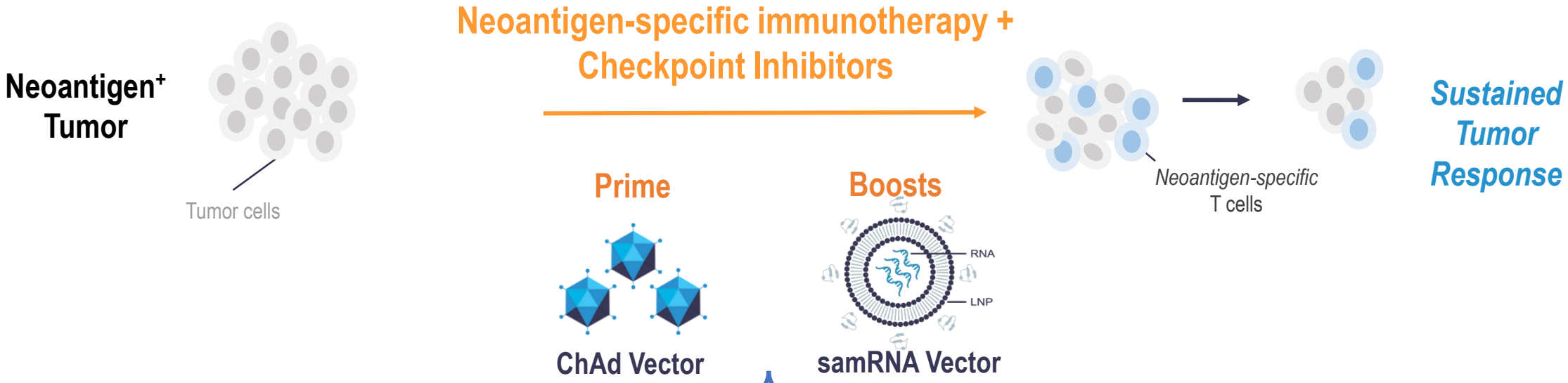
CONSULTING/ADVISORY ROLE

- OncLive®
- Scenic Immunology B.V.

Research Funding to Institution: Bristol Myers Squibb, Merus, and Gritstone bio, Inc.

Study sponsored by Gritstone bio, Inc.

SLATE: Delivering Shared Neoantigens Using an Off-the-Shelf, Heterologous Prime-Boost Vaccine Platform; Evolving to Target KRAS Neoantigens Exclusively



Version 1

G12V G12D G12C x 20 total mutations

Single copies of KRAS, TP53, β-catenin, and other mutations

→ Phase 1 & 2

SLATE-KRAS

G12C x 4 G12D x 4 G12V x 4 Q61H x 4

Repeated copies of KRAS mutations

→ Phase 2

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Study Design: SLATE/GO-005: Phase 1/2 Study Evaluating the Safety, Immunogenicity, and Clinical Activity of Shared Neoantigen Vaccines in Combination with Immune Checkpoint Blockade (ICB)

INCLUSION REQUIREMENT (illustrative examples)	PHASE 1: DOSE ESCALATION	PHASE 2: EXPANSION Efficacy in Solid Tumors	PRIMARY OBJECTIVES
KRAS: G12D, G12C, G12V, Q61H × HLA: A* 01:01, A* 02:01, A* 11:01, A* 03:01, C* 01:02, C* 08:02	Up to 4 Dose Levels Prime: 10^{12} vp ChAd Boost : 30 → 300 ug samRNA +/- 30 mg Ipilimumab (subcutaneous) + 480 mg Nivolumab (intravenous)	Cohort 1: *MSS-CRC-1L maintenance* Cohort 2: *MSS-CRC* Cohort 3: *NSCLC- Post ICB* Cohort 4-6 : *Other tumor types*	Safety and Tolerability Phase 2: Overall Response Rate Recommended Phase 2 Dose
	COMPLETED N= 19	ONGOING N=19 (n=7 with v1; n=12 with SLATE-KRAS)	

MSS-CRC= Microsatellite-stable Colorectal Cancer

NSCLC= Non-small cell lung cancer

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Demographics: Patients Enriched for NSCLC (post-ICB) and MSS-CRC (post-FOLFOX/FOLFIRI)

Demographics and Tumor Type	Version 1 N=26	SLATE-KRAS N=12	Overall N= 38
Age: mean years (min, max)	60 (33, 83)	59 (36, 86)	60 (33,86)
Gender (Male/Female)	10/16	4/8	14/24
Tumor Types			
Non-small Cell Lung Cancer (NSCLC)	13	5	18
No. Prior therapy (median, range)	1 (1-4)	2 (1-3)	1.5 (1-4)
Prior anti-PD-(L)1 therapy	13	5	18
Microsatellite-Stable (MSS) Colorectal Cancer	6	7	13
No. Prior therapy (median, range)	1.5 (1-2)	1 (1-2)	1 (1-2)
No. Prior Oxaliplatin/Irinotecan	6	6	12
Pancreatic Ductal Adenocarcinoma (PDA)	5	0	5
No. Prior therapy (median, range)	1 (1-3)	0	1 (1-3)
Other	2	0	2
No. Prior therapy (median, range)	3 (3)	0	3 (3)

Data cut-off for this presentation: 20 June 2022

Safety: Treatment-Related AEs by SLATE v1 and SLATE-KRAS (> 10%) in Previously Treated Metastatic Solid Tumor Patients

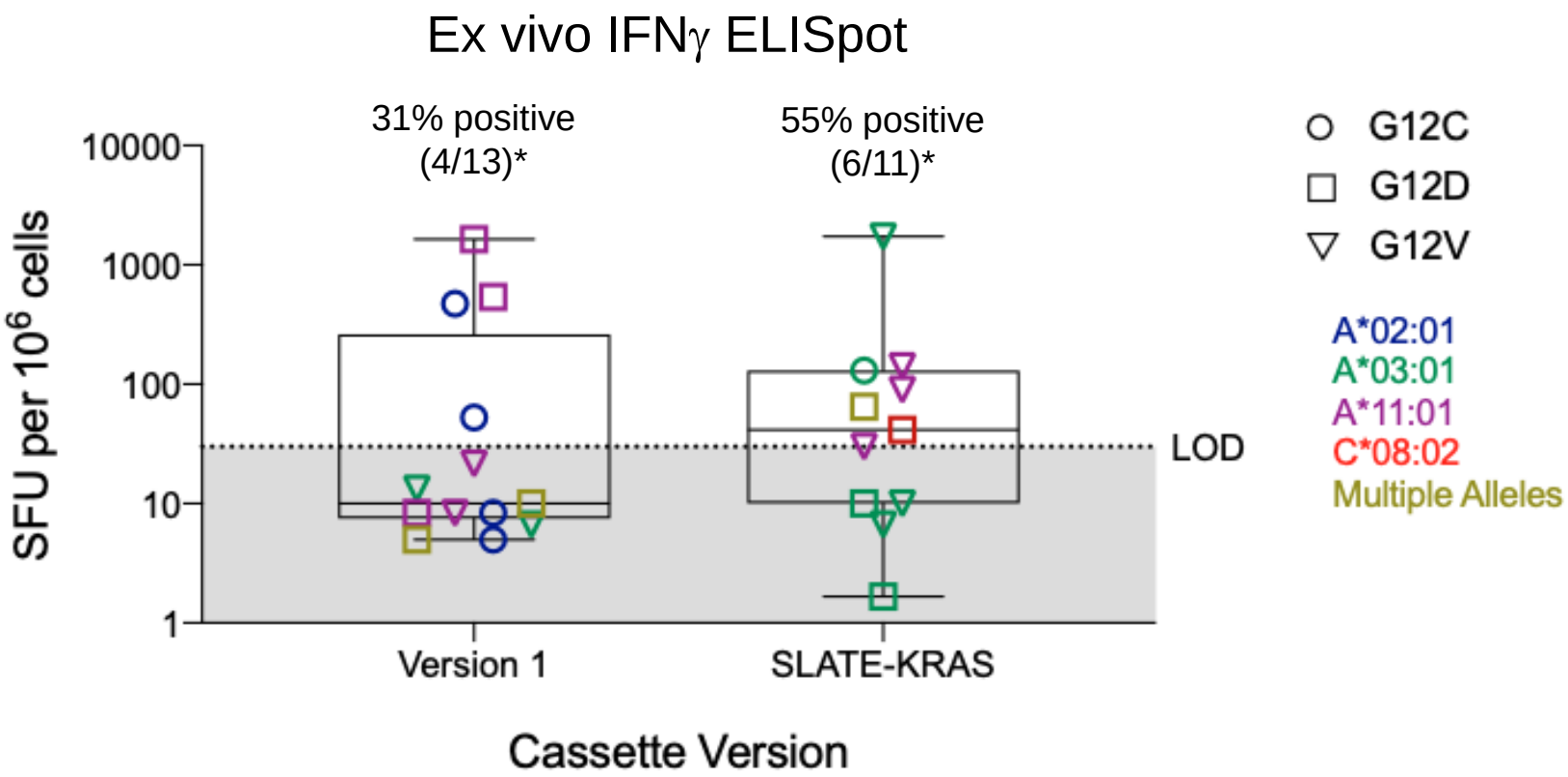
	v1 (n=26)		SLATE-KRAS (n=12)		Overall (n=38)
Preferred Terms; n(%)	Grade 1/ 2	≥Grade 3	Grade 1/ 2	≥Grade 3	All Grades
Pyrexia	14(53.8)	0.0	3(25.0)	0.0	17(44.7)
Fatigue	8(30.8)	1(3.8)	2(16.7)	0.0	11(28.9)
Nausea	6(23.1)	0.0	3(25.0)	0.0	9(23.7)
Vomiting	7(26.9)	0.0	1(8.3)	0.0	8(21.1)
Chills	3(11.5)	0.0	4(33.3)	0.0	7(18.4)
Diarrhoea	5(19.2)	0.0	1(8.3)	0.0	6(15.8)
Myalgia	2(7.7)	0.0	3(25.0)	0.0	5(13.2)
Decreased appetite	2(7.7)	0.0	2(16.7)	0.0	4(10.5)
Injection site pain	2(7.7)	0.0	2(16.7)	0.0	4(10.5)
Injection site reaction	4(15.4)	0.0	0.00	0.0	4(10.5)

Treatment-related Grade 3/4 AEs with frequency <10%:

- With v1, one patient experienced transient Grade 3 increase in alanine aminotransferase and aspartate aminotransferase
- With v1, one patient had Grade 3 confusional state associated with pyrexia

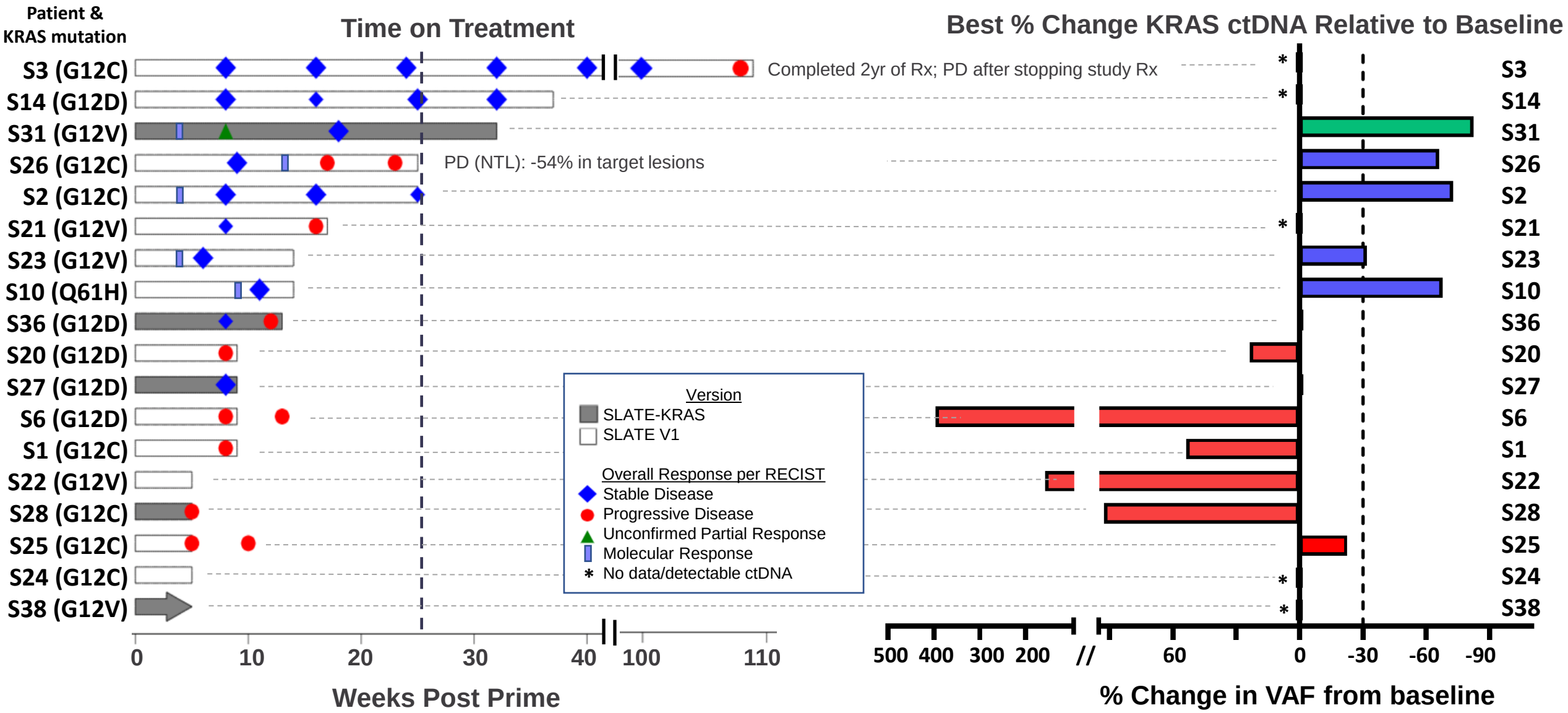
Immunogenicity: Induction of KRAS-specific CD8+ T cells increased with SLATE-KRAS relative to SLATE v1 based on IFNg ELISpot

SLATE-KRAS increase in number of patients with a positive ELISpot response as well as in the median number of spots



* Ex vivo assay using minimal peptides performed on available samples

Efficacy in NSCLC: Early Signals of Durability and Molecular Response in NSCLC Post-ICB



PD= Progressive Disease; VAF = variant allele frequency

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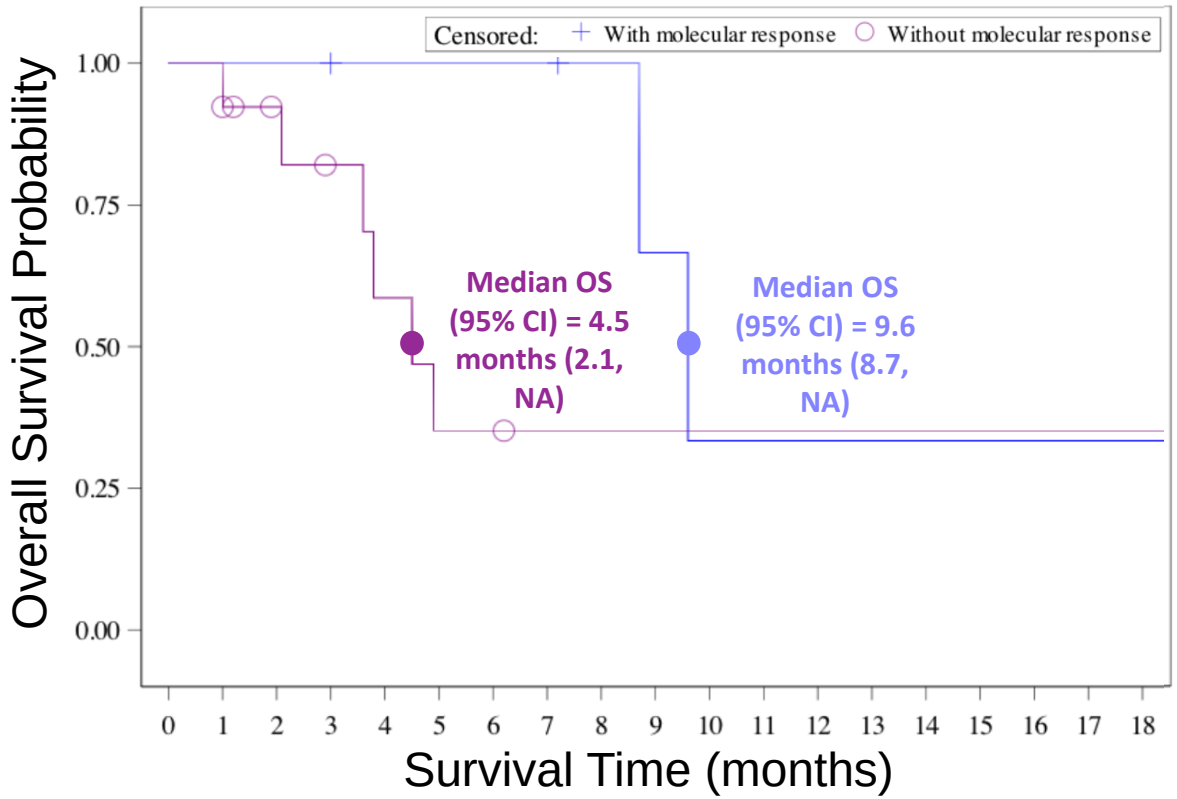
Overall Survival: Trend of Improved Overall Survival in Patients with NSCLC Treated with SLATE-KRAS or SLATE v1 Achieving a Molecular Response Compared to Those Without



Number at Risk				
With molecular response	5	4	1	1
Without molecular response	13	3	2	2

Molecular response = reduction in ctDNA ≥ 30% from baseline

NA = Not achievable

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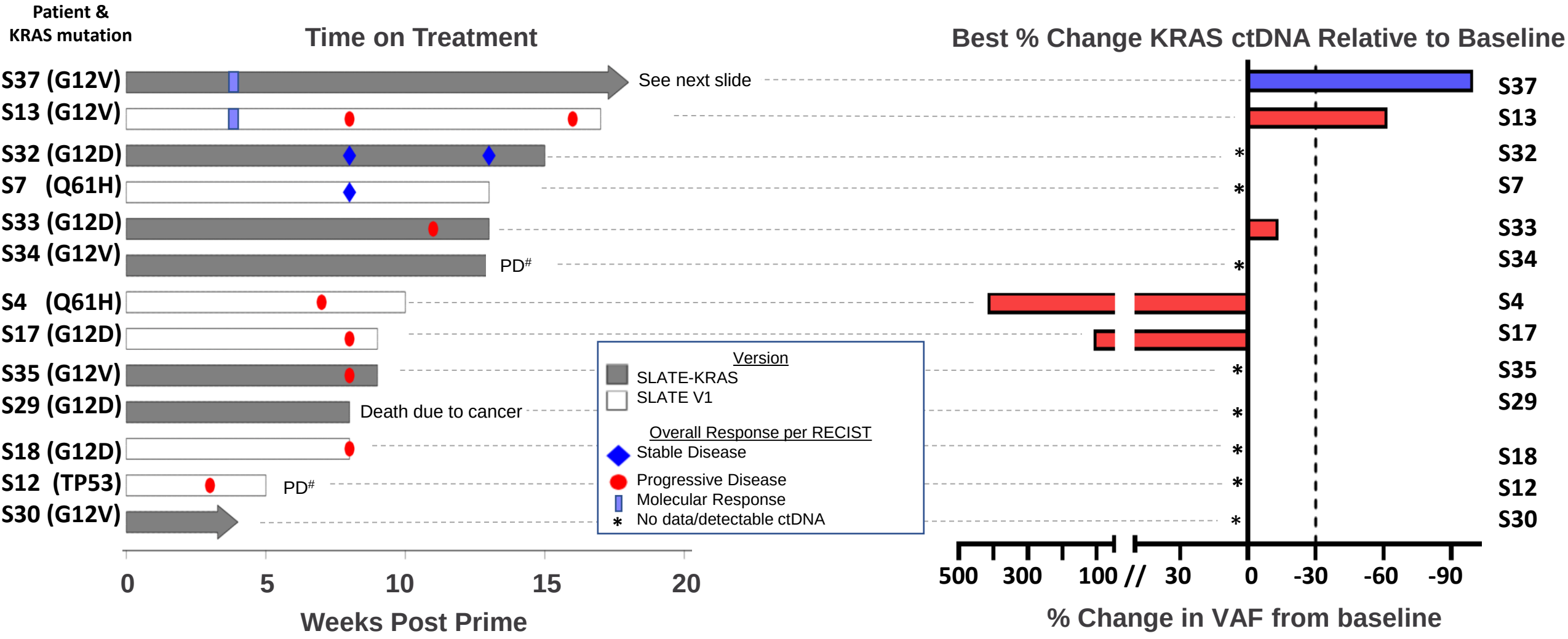
Efficacy in CRC: Early Signal of Durability and Molecular Response in Late-Stage CRC



Patient had progressive disease; incompletely captured in clinical database at time of data cut-off

PD= Progressive Disease; VAF = variant allele frequency

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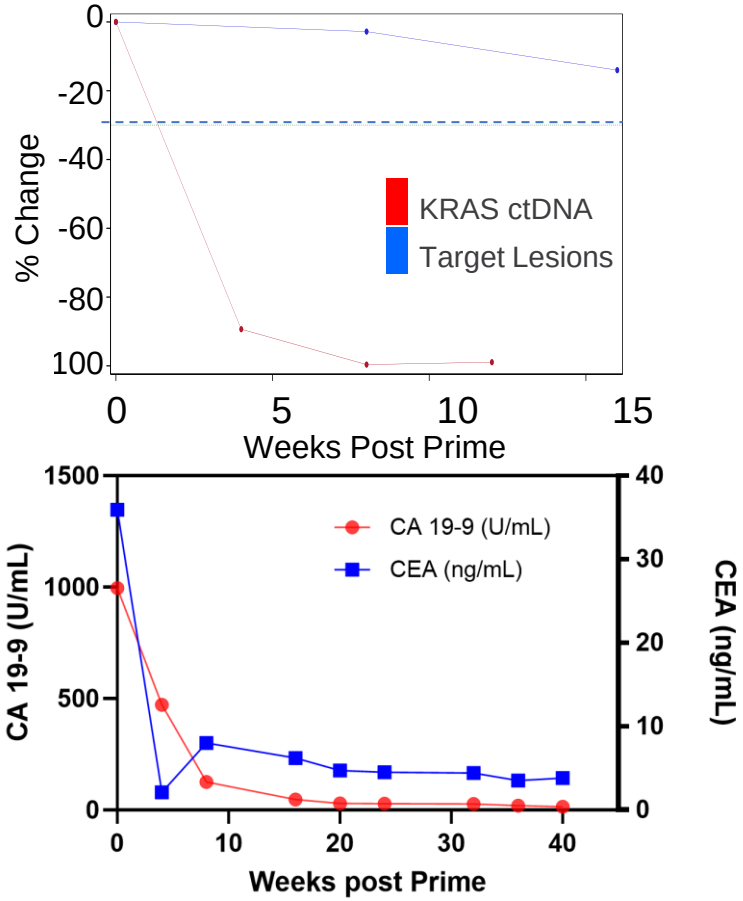
Patient Spotlight S37: 64 yo Female CRC Patient: Molecular Response More Sensitive Indicator of Clinical Benefit over RECIST

Stage IV MSS-CRC
KRAS G12V/HLA-A*11:01

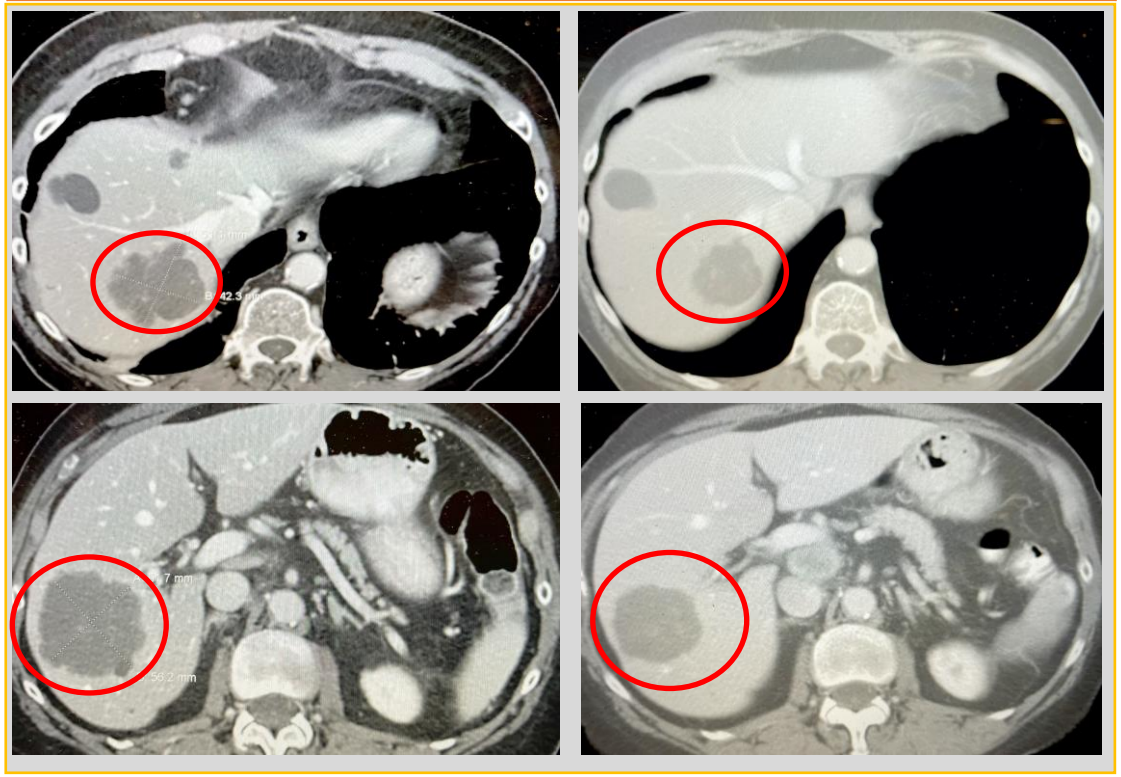
FOLFOX/FOLFIRI/BEV
23 mo (PD)

SLATE-KRAS
Treated beyond PD @24 wks
(RECIST PD due to enlarged lymph node after ChAd boost per PI communication)



CA 19-9 and CEA data obtained after data cut-off

Baseline	Week 24
107 mm	82 mm (-23% relative to baseline)



On Tx biopsy (liver) = 95% necrosis

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Conclusions and Future Directions

Safety and Tolerability

- Heterologous prime-boost neoantigen directed v1 and SLATE-KRAS is well-tolerated in advanced solid cancer patients

Mechanistic Insights

- SLATE vaccine is capable of eliciting KRAS neoantigen-specific $CD8^+$ T cell responses.
- Evidence of immune infiltration into tumor tissue following study treatment (tumor RNAseq data not shown)
- SLATE-KRAS specific cassette elicits stronger $CD8^+$ T cell responses to KRAS mutants compared to v1

Clinical Benefit

- Early evidence of efficacy with both SLATE vaccines in patients with NSCLC who progressed on standard of care with prior anti-PD-(L)1 therapy
  - Molecular (ctDNA) response correlates with improved overall survival
- Molecular response (reduction in ctDNA*) observed in 39% (7/18) of patients with CRC and NSCLC preceding clinical benefit
- Molecular and clinical benefit in patient with KRAS G12V mutant CRC who progressed on 2 prior therapies
- Molecular response may be a superior biomarker of benefit versus RECIST radiology with this novel immunotherapy

Enrollment and treatment continues; results suggest targeting earlier lines of therapy may be beneficial

*Patients with detectable ctDNA at baseline and at least 1 post-baseline sample

ACKNOWLEDGEMENTS

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