Final data from the Phase 2a single arm trial of SurVaxM for newly diagnosed glioblastoma

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2037 Abstract

PURPOSE: Despite intensive treatment with surgery, radiation therapy, temozolomide (TMZ) chemotherapy, and tumor treating fields (TTF), mortality of newly diagnosed glioblastoma (nGBM) remains very high. SurVaxM is a peptide vaccine conjugate that has been shown to activate the immune system against its target molecule survivin, which is highly expressed by glioblastoma cells. We conducted a phase 2a, open label, multi-center trial evaluating the safety, immunological effects, and survival of patients with nGBM receiving SurVaxM plus adjuvant TMZ following surgery and chemoradiation (NCT02455557).

PATIENTS AND METHODS: 63 patients with resected nGBM were enrolled, comprised of 38 males/25 females, 20-82 years old. Following craniotomy and fractionated radiation therapy with concurrent TMZ, patients received 4 doses of SurVaxM (500mcg every 2 weeks) in Montanide-ISA-51 plus sargramostim (GM-CSF) subcutaneously. Patients subsequently received adjuvant TMZ and maintenance SurVaxM concurrently until progression. Progression free survival (PFS) and overall survival (OS) are reported. Immunological responses to SurVaxM were also assessed.

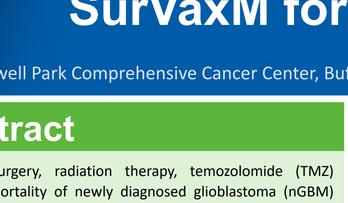
RESULTS: SurVaxM plus TMZ was well-tolerated with no serious adverse events attributable to SurVaxM. Median PFS (mPFS) was 11.4 months and median OS (mOS) was 25.9 months measured from first dose of SurVaxM. A strongly positive correlation, accounting for censoring, was observed between PFS and OS (r=0.79). SurVaxM produced survivin-specific CD8+ T-cells and antibody/IgG titers. Apparent clinical benefit of SurVaxM was observed in both methylated and unmethylated MGMT patients.

CONCLUSION: SurVaxM appeared to be safe and well-tolerated. The combination represents a promising therapy for nGBM, including for those patients with unmethylated MGMT genes. For patients with nGBM treated in this manner, PFS may be an acceptable surrogate for OS. A large randomized clinical trial of SurVaxM for nGBM is in progress.

Background

SurVaxM

- Altered structure 15 amino acid
  - synthetic long peptide
  - Keyhole Limpet Hemocyanin (KLH) conjugate
- Subcutaneous injection
  - 500mcg SurVaxM
    - emulsified in Montanide ISA 51 VG
    - + 100 mcg local Sargramostim (GM-CSF)
  - q2wk x 4, followed by q2m, until progression
- Multi-valency targets several survivin isoforms intracellularly/extracellularly
- Multi-modality stimulates both T cell (CD8/CD4) & antibody (IgG) mediated immune responses



Trial overview

Trial objective:

- Evaluation of 6 month progression free survival (PFS6) in 63 patients treated with SurVaxM + standard of care TMZ, multisite study at 5 US Cancer Centers

Primary endpoint:

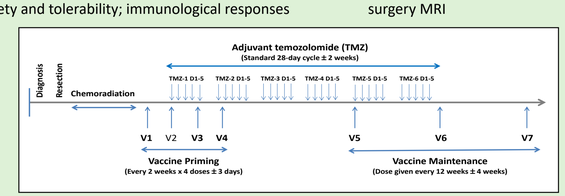
- Progression-free survival at 6 months (PFS6)

Secondary endpoints:

- mPFS & mOS measured from first SurVaxM dose
- Safety and tolerability; immunological responses

Eligibility criteria:

- Newly diagnosed glioblastoma (nGBM)
- ≥18 years of age
- KPS ≥70
- Survivin expression by IHC (≥1%)
- HLA-A*02, A*03, A*11, A*24 MHC-I alleles
- ≤1 cm^3 of residual tumor on 72h post-surgery MRI



Survival – PFS & OS

Survival outcomes measured from start of treatment.

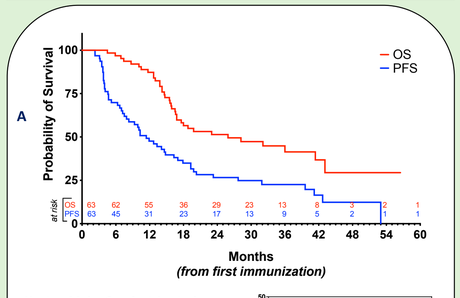
PFS6	PFS12	PFS24	PFS36
69.8%	47.6%	26.6%	22.6%
CI:(56.8,79.5)	CI:(34.9,59.3)	CI:(16.4,37.9)	CI:(12.9,33.9)

	OS12	OS24	OS36
	87.2%	51%	41.4%
	CI:(76.1,93.4)	CI:(38.3,63.0)	CI:(27.8,54.5)

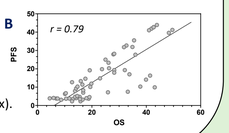
	median Progression Free Survival (mPFS)	median Overall Survival (mOS)
All Patients	11.4 mos.	25.9 mos.

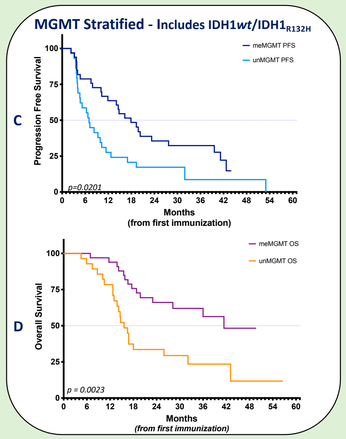
	mPFS	mOS
MGMT Stratified - Includes IDH1wt / IDH1$_{R132H}$		
un-MGMT	7.0 mos.	16.5 mos.
me-MGMT	17.9 mos.	41.4 mos.

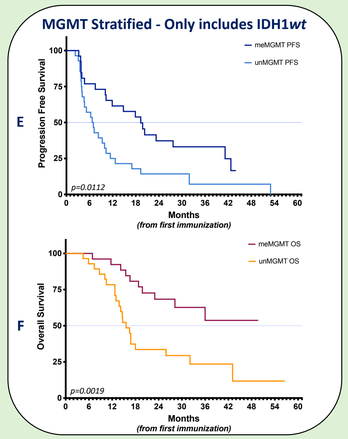
	mPFS	mOS
MGMT Stratified - Only includes IDH1wt		
un-MGMT	6.9 mos.	15.6 mos.
me-MGMT	19.3 mos.	NR (41.4+) mos.



Kaplan-Meier Survival Analysis.
(A) OS vs. PFS for all patients;
(B) Correlation of OS & PFS;
(C,D) MGMT stratification;
(E,F) MGMT/IDH1*wt* stratification;
Significance by Log-Rank (Mantel-Cox).





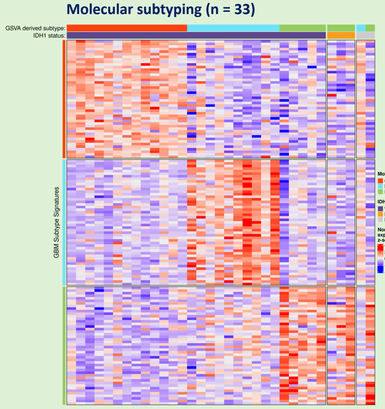


Patient Characteristics & Safety

Patient characteristics

Total patients (n = 63)		
Gender	Male	38 (60%)
	Female	25 (40%)
Age	Mean	56.5
	Median	60
	Range	20-82
KPS score	Median	90
	Range	70-100
MGMT Status	Unmethylated	29 (46%)
	Methylated	33 (52%)
	Unknown	1
IDH status	*wild type*	53 (84%)
	IDH1-R32h	8 (13%)
	Unknown	2
% SVN (IHC)	Mean	12.7%
	Median	12%
	Range	1%-40%
Haplotype	A*02/A*02	19 (30.2%)
	A*02/A*03	8 (12.7%)
	A*01/A*02	6 (9.5%)
	A*03/A*03	5 (7.9%)
	A*02/A*24	4 (6.3%)
	A*02/A*11	4 (6.3%)
	A*24/A*24	4 (6.3%)
	Other	13 (20.6%)

Molecular subtyping (n = 33)

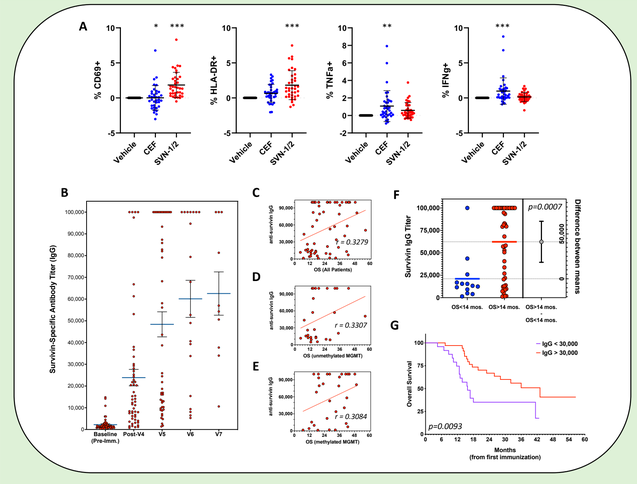


Molecular subtypes of patient tumors (n=33). RNA was extracted from tumor tissue, then subjected to paired-end bulk sequencing (Tempus) and alignment to reference genome GRCh38. Gene Set Variation Analysis showed patient population was consistent with the molecular spectrum of nGBM previously reported Wang, *et al.*[1]

Adverse events & toxicities

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	1			
Amnesia	12			
Arthralgia	3			
Asthenia		1		
Back Pain	1			
Chills	1			
Confusion			1	
Decreased appetite	1	1		
Fatigue	12	1		
Hyperhidrosis	1			
Hypersensitivity				
Hypertension		1		
Influenza-like illness	7			
Injection site haematoma	5			
Injection site induration	5			
Injection site pain	12			
Injection site pruritus	2			
Injection site reaction	37	3		
Injection site swelling	2			
Lymphopenia	2	6	1	1
Malaise	2			
Myalgia	4	1		
Nausea	1			
Neutrophil count decreased	2	2		1
Panniculitis		2		
Paresthesia	3			
Platelet count decreased	2			
Pruritus	2	1		
Pyrexia	5			
Rash	2	1	1	
Rash maculo-papular			1	
Skin hypertrophy	1			
Subcutaneous nodule	3			
Transaminases increased		1		
Urticaria	1	1		
Leukopenia	4			

Immunological Responses



Immunological responses. (A) Patient CD8+ T cell activation by SurVaxM epitope peptides (SVN-1/2) or positive control peptide (CEF). PBMC harvested at ~17 weeks (dose V5). CD3+/CD8+ gated activation markers and/or cytokine expression are compared to vehicle (unstimulated); *$p<0.05$; **$p<0.005$; ***$p<0.0005$. **(B)** Patient anti-SurVaxM IgG titers (baseline; V4-V7) by indirect ELISA. **C-E.** Correlation of OS & anti-SurVaxM IgG titers in **(C)** all patients, **(D)** unMGMT & **(E)** meMGMT. **(F)** Mann-Whitney comparison of IgG titers at OS <> 14 mos; (G) Kaplan-Meier Survival Analysis, comparison of IgG titer <> 30,000 by Log-Rank (Mantel-Cox) (n=58). **IgG > 30,000 = OS 43.1 mos. (n=34), IgG < 30,000 = OS 15.8 mos. (n=24).**

Conclusions

- PFS6 measured from first SurVaxM treatment was 69.8% (CI; 56.8, 79.5), significantly greater ($p < 0.0001$), than historical control PFS6 of 37%.[2]
- PFS and OS were strongly correlated (accounting for censoring) amongst treated patients ($r = 0.79$; (CI; 0.66, 0.87)).
- SurVaxM was well tolerated with no serious adverse events attributed to vaccine.
- SurVaxM showed clinical benefit in both methylated and unmethylated MGMT.
- Patients mounted antibody (IgG) & CD8+ T cell responses responses to SurVaxM,
  - Those with OS > 14 months had significantly greater anti-Survivin IgG titers (>30,000) compared to patients with OS < 14 months (p=0.0007).
- ***A Randomized, Blinded, Placebo-Controlled Phase 2b Trial of SurVaxM for Newly Diagnosed Glioblastoma (SURVIVE) is currently recruiting.***

References & Acknowledgments

References:
1. Wang Q, Hu B, Hu X, et al. Cancer Cell 32:42-56 e6, 2017
2. Stupp R, Taillibert S, Kanner A, et al. JAMA 318:2306-2316, 2017

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MimiVax, LLC, holds the worldwide license for development of SurVaxM. MSA, MJC & RAF are equity shareholders of MimiVax

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