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REVIEW

Efficacy and Safety of Actively Personalized Neoantigen Vaccination in the Management of Newly Diagnosed Glioblastoma: A Systematic Review

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Purpose: Glioblastoma (GBM) shows frequent relapse and is highly resistant to treatment; therefore, it is considered fatal. Various vaccination protocols that have been tested in patients with GBM, which is the most common and aggressive primary brain tumor, have indicated safety and efficacy, to some extent, when used alone or in combination with standard of care. Recently, neoantigen-based personalized vaccines have shown tremendous immunogenicity and safety in GBM. We aimed to systematically review the medical literature for clinical trials to evaluate the efficacy and safety of neoantigen-based personalized vaccines for newly diagnosed GBM.

Methods: We conducted a literature search for clinical trials on PubMed, Cochrane Library, China National Knowledge Infrastructure, and ClinicalTrials.gov until March 20, 2021. The primary outcomes of interest were immunogenicity and safety of the therapy. Efficacy outcomes, such as progression-free survival and overall survival, were secondary outcomes of interest.

Results: Two clinical trials involving 24 patients were included in this review. High immunogenicity was observed in both studies. The GAPVAC-101 trial reported 50% APVAC1-induced and 84.7% APVAC2-induced immunogenicity with CD8+ and CD4+ T cell responses in 92% (12/13) and 80% (8/10) immune responders, respectively. Two out of five patients showed CD4+ and CD8+ T cell responses in the study by Keskin et al. Dexamethasone use had limited immunogenicity in a trial by Keskin et al (6/8). No serious treatment-related adverse events were reported.

Conclusion: Actively personalized vaccines aimed at unmutated peptides and neoantigens for patients with GBM are safe and highly immunogenic, particularly when administered in combination. Larger studies are warranted to investigate the role.

Keywords: glioblastoma, GBM, active immunotherapy, personalized peptide vaccination, neoantigen, immunogenicity, safety

Introduction

Glioblastoma multiforme (GBM) accounts for 14.9% of primary brain tumors and 55.4% of all gliomas, but it is the most common (46.6%) of all malignant tumors of the central nervous system. Its incidence rate is 3.20 per 100,000 population. According to the CBTRUS Statistical Report 2009–2013, GBM is significantly prevalent in males compared to that in females and in whites compared to that in blacks in the United States.[1] GBM exists in the primary and secondary forms. Primary GBM, which represents the majority of the tumors (90%), develops de

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novo and has no lower grade precursor malignancy. Secondary GBM is a grade IV glioma and has low-grade diffuse astrocytoma (grade II) or anaplastic astrocytoma (grade III) as its precursor.[2] Clinical manifestations of GBM include physical, neurological, and psychological signs and symptoms, such as headache, nausea and vomiting, visual and language disturbances, motor weakness, cognitive impairment, memory loss, and personality changes.[3]

GBM is considered fatal because it frequently relapses and is highly resistant to therapy.[4] Patients with GBM who have not received treatment reported a median survival time of only 3 months.[5] Standard of care (SOC), which consists of surgical resection, temozolomide chemotherapy, and radiotherapy, has improved the median survival time to 12–18 months.[5,6] Targeted therapy involving the addition of bevacizumab and everolimus to the SOC has comparatively improved outcomes.[7,8] Recent advances in immunotherapy, especially immune checkpoint inhibitors (ICIs), have shown promise for several cancers. However, monotherapy with ICIs has failed to improve outcomes in patients with GBM.[9] Hence, GBM is also termed as a "cold tumor." However, several forms of vaccinations have been administered for GBM, which have shown a slight surge in progression-free survival (PFS) and overall survival (OS) in these patients.[10]

Three main types of antigens that are targeted in GBM vaccinations are being tested clinically. They include tumor-associated antigens (TAAs), tumor-specific antigens (TSAs), and tumor lysate.[11] Neoantigens are TSAs resulting from somatic DNA alterations in the form of nonsynonymous point mutations, insertions or deletions, gene fusions, and frameshift mutations. Most recently, there has been a boom in the application and success of neoantigen-based vaccination for melanoma.[12] Moreover, in other cancers, such as melanoma, colorectal cancer, and non-small cell lung cancer (NSCLC), somatic mutation burden was correlated with increased survival and clinical benefit derived from ICI application.[13–17] This vaccine represents a more personalized form of vaccine, as it accounts for cancer-to-cancer variation for specific cancer types as well as patient-to-patient variations. Recently, two trials have assessed neoantigen-based peptide vaccines for newly diagnosed patients with GBM. Both these trials have reported tremendous CD8+ and CD4+ T cell responses against the tumor and tumor infiltration of these cells, making them "hot tumors."[18,19] We aimed to conduct a systematic review of studies to evaluate the efficacy and safety of neoantigen-based vaccines for GBM, keeping in mind the future prospects.

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting.[20] A protocol of this study is registered on PROSPERO: CRD42021248719.

Inclusion Criteria

Patients and Study Types

Patients with GBM who received personalized neoantigen vaccines were included. Only clinical trials (CTs) were included in this study. Retrospective studies, case reports, and/or commentary were excluded.

Types of Interventions

The intervention was personalized neoantigen-based vaccine for patients with GBM.

Outcomes of Interest

Immunogenicity and safety were the primary outcomes of interest. The secondary outcomes of interest included PFS and OS.

Search Strategy

Databases

We conducted a literature search in PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), and ClinicalTrials.gov until August 20, 2019. "English only" language restriction was applied. Furthermore, references of relevant studies were searched for identifying more studies.

Study Selection

The selected studies were imported into Endnote X9 software for organizing, screening, and removing duplicates. After removal of duplicates, the titles and abstracts of the studies were screened. Studies that met the exclusion criteria were excluded. Study selection was performed by two independent reviewers. Full text and supplementary materials were obtained for the selected studies. Any disagreements were resolved by discussion among the authors' team.

Data Extraction

The Cochrane Collaboration Data Collection form—randomized controlled trials (RCTs) and non-RCTs—was used and modified for data extraction. We collected information on attributes of the studies, study design, first

author, country of research, publication year, number of participants, and characteristics of vaccine development and delivery. Characteristics of patients, such as age, Karnofsky Performance Scale (KPS), human leukocyte antigen (HLA) allotypes, MGMT methylation status, and median number of vaccinations. Finally, data of the outcomes of interest were extracted, which included data on immunogenicity and safety and patient survival.

Assessment of Risk of Bias

Risk of bias was assessed using the Cochrane tools.[21]

Measurement of Treatment Effect and Data Synthesis

The extracted data were incorporated into the table form. Immunogenicity was recorded as the number of immunogenic peptides, observed CD8+ and CD4+ T cell responses, and tumor infiltration of T cells.

Results

Studies' and Patients' Characteristics

Two CTs involving 24 patients were included in this systematic review (Figure 1).[18,19] All patients had newly diagnosed GBM and had received surgery, radiotherapy, or chemoradiotherapy, followed by personalized neoantigen-based vaccine. GAPVAC-101 patients (n=16) received two synthesized peptide vaccines, one aimed at unmutated peptides (APVAC1) and the other aimed at neoantigens (APVAC2). APVAC1 was formulated using a pre-constructed library of HLA-presented non-mutated antigens in patients with GBM. APVAC1 consisted of seven best-ranked class I peptides plus two class II (pan-DR antigen) and a viral peptide. The participants (n=8) in Keskin et al's study received only a neoantigen-based vaccine formulation (NeoVax). One case study that reported neoantigen-specific T cell responses in a patient

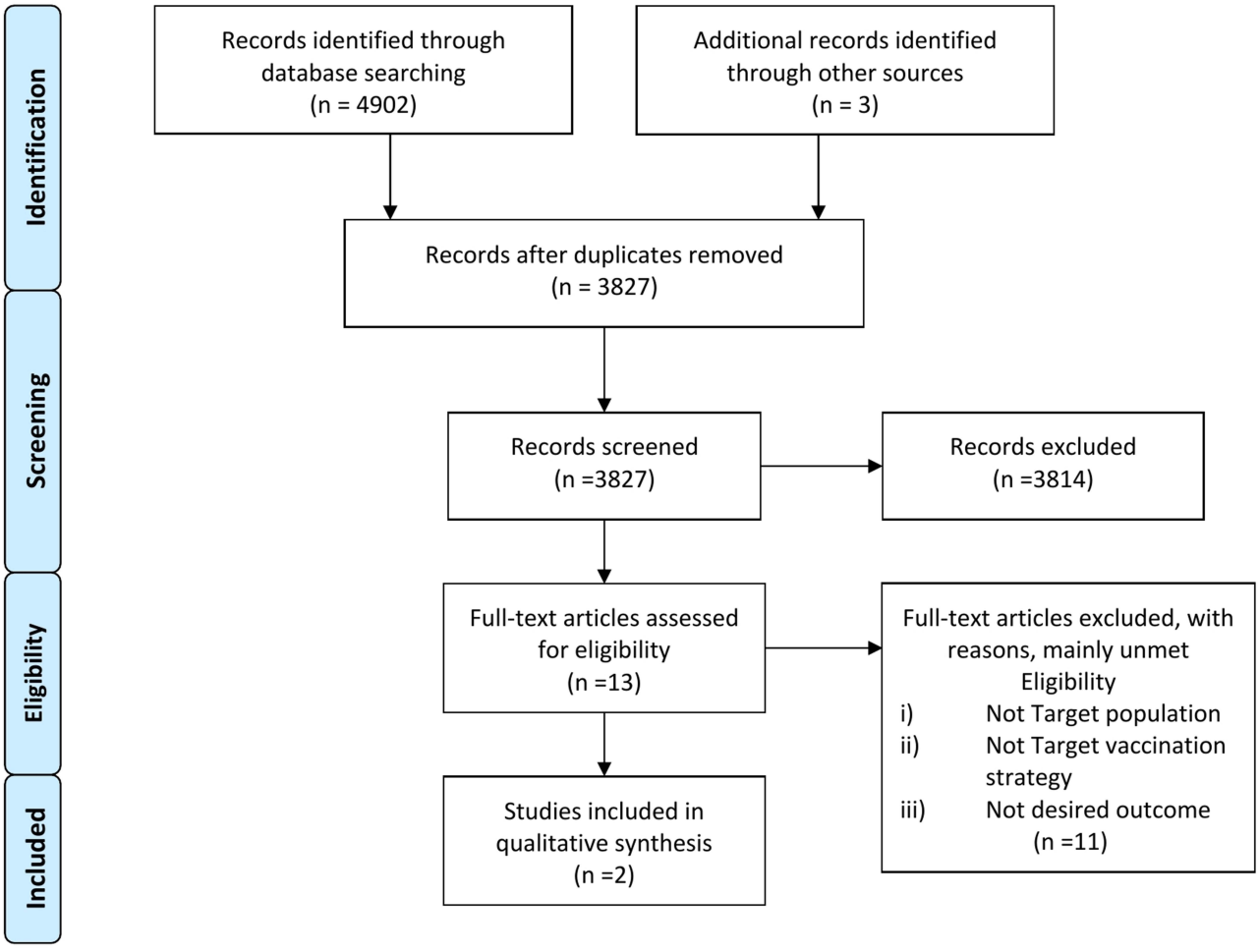

Figure 1 PRISMA flow diagram.

Notes: PRISMA figure adapted from Moher D, Liberati A, Altman D, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health-care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009; 62(10). Creative Commons[20].

with GBM after the administration of neoantigen vaccine was excluded.[22] The general characteristics of the studies, participants, and vaccines are listed in Table 1.

Immunogenicity

Three vaccines (APVAC1, APVAC2, and NeoVax) were applied: 2 (APVAC1 and APVAC2) in the GAPVAC-101 trial and 1 (NeoVax) by Keskin et al. APVAC1 produced 50% immunogenicity, and APVAC2 induced 84.7% immunogenicity. APVAC1 produced CD8+ T cell responses of the central memory type, and APVAC2, which was aimed at neoantigens, produced primarily CD4+ T cell responses. In the study by Keskin et al, two of the five patients who received at least one boost after priming but did not receive dexamethasone for side effects at priming showed immunogenicity. Keskin et al also revealed that both kinds of responses of CD4+ T cells and CD8+ T cells enriched in the memory phenotype (Table 2).

APVAC1

A total of 13 patients received 87 APVAC1 peptides. Eleven of the 13 patients showed immunogenicity with sustained immune responses of central memory CD8+ T cells. Forty-five of the 87 vaccination peptides were immunogenic, revealing a 51.7% immunogenicity. Each APVAC1 had two peptides directed at class II antigens (pan-DR antigens). Overall, 13 patients had received 26 peptides, of which 9 showed immunogenicity to one or both unmutated pan-DR antigens. Thirteen of the 26 peptides administered were immunogenic, revealing 50% immunogenicity. These peptides mainly induced CD4+ T cell responses.

APVAC2

Overall, ten patients were evaluated for APVAC2 immunogenicity. Eight patients (80%) demonstrated neoepitope-specific immune responses, predominantly CD4+ T cell responses. Eleven mutated APVAC2 peptides induced isolated CD4+ T cell responses or CD4+ plus CD8+ T cell responses of the 13 vaccinated individuals, showing an 84.7% immunogenicity. The CD4+ T cell responses were predominantly of the T_H1 phenotype and were multifunctional. None of these mutated APVAC2 peptides had induced isolated CD8+ T-cell responses. APVAC2 unmutated peptides[6] induced CD8+ T cell responses only once (Patient 8).

NeoVax

Overall, two patients who did not receive dexamethasone showed immunogenic responses. Patient 7 primarily responded to pool C peptides with CD4+ T cell responses, primarily against the mutated neoepitopes. Patient 8 responded to two pools (pools A and B) with CD4+ T cell responses against three neoepitopes. Two mutated neoepitopes were targeted preferentially over the wild type, whereas 1 (COX18) neoepitope showed similar reactivity between mutant and wild type. Approximately 20–30% of the CD4+ and CD8+ T cell responses were polyfunctional, and half of these expressed at least one effector cytokine.

Tumor Infiltration of T Cells

Both studies revealed tumor infiltration of CD8+ and CD4+ T cells. GAPVAC-101 reported that a single patient (Patient 8) had tumor resection following recurrence at 26.8 months after diagnosis, demonstrating high infiltration of T cells and a favorable CD8+ T/FOXP3+ Treg cell ratio. Keskin et al reported five patients (Patients 3, 4, 5, 7, and 8) with disease progression (PFS; median=17.3 weeks; range, 6.7–26.3) underwent surgery after vaccination. Two patients (Patients 7 and 8) showed a significant increase in CD8+ T cell infiltration into the tumor at relapse compared to that at baseline (p=0.006). Compared to Patients 3, 4, and 5 who received dexamethasone, Patients 7 and 8 demonstrated an increase in CD8+ (p=0.02) and CD4+ T cells (p=0.008).

Safety and Tolerability

Both studies reported treatment-related adverse events. Injection site disorders were the prominent side effects, particularly in the GAPVAC-101 study. Other events were mild (Table 3).

Progression-Free Survival and Overall Survival

Both studies reported PFS for all participants. Keskin et al revealed a median PFS of 7.6 months (n=8). The GAPVAC-101 study reported a median PFS of 14.2 months (n=15). A median OS of 29 months was reported in the GAPVAC-101 study, whereas Keskin et al reported a median OS of 16.8 months.

Checkpoint Inhibition Compatibility

ICIs when administered as monotherapy have failed in GBM treatment.[9] However, it is anticipated to be an adjuvant with personalized neoantigen-based vaccine, as

Table 1 General Characteristics of the Studies and Patients

Clinical Trials	Keskin et al[19]	GAPVAC-101[18]	Total
Characteristics			
Number of participants Age (median; years) Female	N=8 (100) 65 (range, 45–73) 6 (75)	N=16 (100) 52.5 (range, 25–70) 7 (44)	24 (100) 13 (54)
KPS			
100 90 80 70	0 6 (75) 1 (13) 1 (13)	4 (25) 6 (37.5) 5 (31.25) 1 (6.25)	4 (16.6) 12 (50) 6 (25) 2 (8.3)
MGMT methylation	MGMT unmethylated	28.6% MGMT hypermethylated	
IDH1 wild-type	8 (100)	-	
Dexamethasone use	6 (75)	1	7 (29)
Mutations per tumour (median; range)	59 (32–93) Coding mutations per tumour	36 (19–84) somatic, non-synonymous mutations	
Surgery to 1st neovax (median weeks; range)	18.6 (17.1–25.0)		
Vaccine composition	**NeoVax:** 7–20 peptides (15–30aa) divided into pools of 3–5 peptides (9–10aa) designated as A, B, C, D	**APVAC1:** 7 class I peptides + 2 class II peptides + a viral marker peptide **APVAC2:** 20 de novo synthesized peptides (14 mutated and 6 unmutated)	
Adjuvant	Admixed with poly-ICLC	GM-CSF (intra- dermal injection) and poly-ICLC (subcutaneous injection)	
Vaccination peptides/ patient (median; range)	12 (7–20)	APVAC1/2: 12/10	
HLA-restriction	None	HLA-A*02:01 HLA-A*24:02	

Note: All data given as frequencies and (percentages) unless otherwise indicated.
Abbreviations: N, number; MGMT, O[6]-methylguanine-DNA methyltransferase, IDH1= isocitrate dehydrogenase 1; HLA, human leukocyte antigen; poly-ICLC, poly-inosinic and polycytidylic acid, stabilized with poly-l-lysine and carboxymethylcellulose; GM-CSF, granulocyte–macrophage colony-stimulating factor; HLA-A*02/ HLA-A*24, human leukocyte antigen serotype determined by the antibody recognition of the α2 domain/α^{24} subset of the HLA-A α-chain.

the new T cell responses disappear owing to T cell exhaustion.[23] Keskin et al revealed the expression of co-inhibitory molecules, such as TIM-3, TIGIT, PD-1, CTLA-4, and LAG-3 in combinations of 2 or 3 on T cells, including both CD4+ and CD8+ T cells. A subset of CD8+ tumor-infiltrating T cells were positive for PD-1 post-vaccination, and their levels increased significantly with vaccination in Patients 7 and 8 (p=0.04). GAPVAC-101 also revealed a mild to moderate increase in PD-1 expression on CD8+ T cells to APVAC1 (n=16) and APVAC2 (Patient 14) post-vaccination.

Dexamethasone Effect

Dexamethasone, as required for treating brain edema in patients undergoing chemoradiotherapy, has been shown to cause immunosuppression by impairment of T cell proliferation (CD4+ and CD8+ T cells).[24] Keskin et al pointed out the use of dexamethasone as the cause of immune unresponsiveness, as patients (n=6) who had required it for treating side effects were unable to show immunogenicity. One patient in the GAPVAC-101 study (Patient 9) also required high-dose dexamethasone and was not evaluable for immunogenicity.

Table 2 Immunogenicity of Personalized Unmutated & Neoantigen Vaccination

Vaccines	Peptides	Number	Immunogenic	Patients	T Cells Responses
APVAC1	Class I	87	45 (51.7%)	12/13 (92.3%)	CD8+ T cells
	Class II	26	13 (50%)	9/13 (69.2%)	CD4+ T cells
APVAC2	Mutated	13	11 (84.7%)	8/10 (80%)	CD4+ and CD4+ plus CD8+ T cells
	Unmutated	6	1 (16.7%)		CD8+ T cells
NEOVAX	7–20 peptides (15–30aa) divided into pools of 3–5 peptides (9–10aa) designated as A, B, C, D	60	Pool C peptides (pt-7) A, B pools (pt-8)	2/5	Mainly CD4+ T cells (Pt 7 and 8) and lower frequencies of CD8+ T cells (only Pt 7)

Table 3 Treatment Related Adverse Events

Adverse Event	All TRAE		Grade >2	Grade ≥3	Total
	GAPVAC-101[18]	Keskin et al[19]	Keskin et al[19]	GAPVAC-101[18]	
Total events	34	9	2	5	43
Chills	2	1			3
Dizziness		1			1
Fatigue	3	1	1		4
Flushing		1			1
Headache	2	1	1		3
Myalgia		2			2
Nausea	2	1			3
Injection site reaction	14	1		1	15
Influenza like illness	3				3
Leukopenia	2			1	2
Anaphylactic reaction	2			1	2
Rash	1				1
Lymphopenia	1			1	1
Brain edema	1			1	1
Skin odor abnormal	1				1

Note: All data given as frequencies.
Abbreviation: TRAE, treatment-related adverse events.

Discussion

A familiar pattern of development is being observed in vaccination-based immunotherapy to overall advancements in cancer therapeutics—from generalized treatment to more personalized therapy. A series of vaccination regimens targeting three main categories of antigens in GBM, namely, TAAs, TSAs, and tumor lysate, were investigated in several trials, which revealed comparative safety and better efficacy.[11] These vaccine protocols included Rindopepimut targeting EGFRvIII (a mutant form of epidermal growth factor receptor present in 20–30% of patients with GBM),[25–28] WT-1 vaccine (Wilm's tumor gene 1) targeting 9-mer modified WT-1 peptide,[29–32] SurVaxM targeting survivin (a glioma cell survival protein),[33] and a prophage (G 100, G200, Vitespen, Oncophage) targeting the heat shock protein peptide

complex (HSPPC-96).[34–36] Rindopepimut alone showed superior PFS and/or OS over temozolomide in matched/historical controls in two preliminary trials (ACTIVATE: n=18; ACT II: n=22) but failed to show any improvement in PFS or OS with the addition of temozolomide (ACT III and ACT IV).[25–28] WT-1 vaccine trials mainly aimed at safety and clinical response evaluations. The results indicated that WT-1 was safe, with evidence of clinical and humoral responses.[29–32] SurVaxM also induces immunogenicity with no safety concerns in recurrent GBM.[33] Likewise, HSPPC-96 vaccine also proved its immunogenicity, with improvement in PFS (median 11 to 17.8 months) and OS (median 23.8 to 31.4 months).[34–36] Gliovax, a vaccine made from autologous antigens of a patient's own tumor in combination with allogeneic antigens from other patients with GBM, revealed 100% 6-month OS in a smaller study (n=9) involving recurrent GBM (rGBM).[37] Dendritic cell-based vaccines pulsed with tumor autologous lysates or tumor-associated multiple epitopes have also been shown to be safe and efficacious in several Phase I and Phase II studies.[38–44] IMA950, a more personalized form of vaccine, was tested using patient-associated antigens found on HLA antigen surface receptors and was also shown to be safe and efficacious.[45] A Phase III study evaluating personalized peptide vaccine, the method that was applied in the GAPVAC-101 trial for unmutated antigen (APVAC1) selection, showed safety but no efficacy compared to the control.[46] More or less, such vaccines alone or their integration into the SOC have shown safety and, to some extent, better efficacy than SOC alone only in smaller trials, as shown in Table 4.

Neoantigens represent a more personalized cancer treatment and patient-specific vaccination. This vaccination has already shown higher immunogenicity and efficacy in patients with melanoma, which carries a higher mutational burden.[47,48] By contrast, GBM represents a less mutation-carrying tumor with low infiltration of intratumoral T cells.[23] Therefore, the results of such high immunogenicity and efficacy, particularly in the GAPVAC-101 trial, show promise for this group of patients. HLA-restricted personalized peptide vaccines (APVAC1) as well as neoantigen-containing peptides (APVAC2) showed 50% and 84.7% immunogenicity and, more importantly, 92% and 80% immune responders, respectively. This study also reported a median overall survival of 29 months, which is higher than that reported in a previous study (Table 4). However, this represents a combination of two vaccine strategies applied for the first time. The HLA-restricted personalized peptide vaccine strategy alone failed to demonstrate any efficacy in a phase III trial for patients with GBM.[46] Similarly, Keskin et al also applied only neoantigen-based vaccines, which demonstrated immunogenicity in only two of the eight patients and an OS of 16.8 months. These studies included a small number of patients, which makes it difficult to analyze the efficacy outcome; nevertheless, a combined approach may provide a better option warranting further exploration in larger trials.

T cell exhaustion through inhibitory checkpoints, such as CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), PD-1 (programmed cell death-1), TIGIT (T cell immunoreceptor with Ig and ITIM domains), and TIM-3 (T cell immunoglobulin domain and mucin domain-3), reflects a post-vaccination scenario for these patients. Both these trials revealed evidence for increased expression of PD-1 on CD8 + T cells (circulating and tumor-infiltrating T cells) post-vaccination.[18,19] Although ICIs when administered as monotherapy have failed in patients with GBM, exhausted CD8+ T cells in GBM could provide the rationale for administering ICIs in combination with personalized vaccine. Although two or three of the co-inhibitory receptors (CTLA-4, PD-1, TIGIT, and TIM-3) were expressed on these immune cells, double checkpoint inhibition of nivolumab and ipilimumab was not safe in patients with GBM.[9] Somatic mutation load has been correlated with deriving clinical benefit from ICIs in multiple cancers, including NSCLC, melanoma, and colorectal cancers, as previously mentioned.[14–17,49] However, in patients with GBM, the mutational/predicted-neoantigen burden was revealed as a biomarker of resistance in a study investigating preclinical efficacy and predictive biomarkers of responsiveness to ICIs.[50] Dexamethasone also upregulates the expression of CTLA-4 and PD-1, but only CTLA-4 blockade hinders dexamethasone-induced immunosuppression.[51] Hence, the addition of ICIs to SOC and vaccination may prolong the survival outcome of patients with GBM. Nonetheless, immune checkpoint inhibition in GBM is challenging and is under investigation with other SOC modalities.[52]

There were some inherent limitations that should be taken into account. Dexamethasone administration may have limited the trial by Keskin et al. Dexamethasone induces immunosuppression through depletion of lymphocytes (CD4+ and CD8+ T cells), impairment of T cell proliferation and differentiation, and increase of regulatory T cell proliferation and activation.[24,46] Therefore, dexamethasone as an anti-inflammatory drug may have

Table 4 Clinical Trials Assessing Safety, Immunogenicity and Clinical Efficacy of Various Types of Vaccines Alone, in Comparison or Together with Other Standard of Care Therapies in Newly Diagnosed or Recurrent Glioblastoma

Studies	Trial Phase, Design, NCT	Population Size	Vaccine Type	Antigen Type	Primary Endpoints	Median PFS (Months)	Median OS (Months)
AVTIVATE[25]	Phase II, multicenter trial	N=18, ND-GBM	Rindopepimut (CDX-110)	EGFRvIII	OS, PFS (+)	14.2	26.0 (95% CI, 21.0 to 47.7)
ACT II[26]	Phase II, multicenter trial	N=22, ND-GBM	Rindopepimut (CDX-110)	EGFRvIII		15.3 (95% CI: 11.0–18.5)	23.6 (95% CI: 18.5–33.1
ACT III[27]	Phase II, multicenter trial	N=65, ND-GBM	Rindopepimut (CDX-110)	EGFRvIII	PFS (+)	9.2 (95% CI: 7.4–11.3)	21.8 (95% CI: 17.9–26.5)
ACT IV[28]	Phase III, randomized, double-blind trial	N=371, ND-GBM	Rindopepimut (CDX-110) + TMZ	EGFRvIII	OS (-)	8.0 (95% CI: 7.1, 8.5)	20·1 (95% CI: 18·5–22·1)
Izumoto et al (2008)[29]	Phase II	N=21, ND-GBM	WT-1 vaccine	9-mer modified WT-1 peptide	Safety, Clinical response (+)	2.8	
Hashimoto et al (2015)[30]	Phase I	N=7, rGBM	WT-1 vaccine	9-mer modified WT-1 peptide	Safety	5.2–49.1	
Oji et al (2016)[31]	Phase II	N=59 GBM	WT-1 vaccine	9-mer modified WT-1 peptide	Humoral response (+)	1.7	5.14
Tsuboi et al (2019)[32]	Phase I	N=14, rGBM HLA-A*24:02-positive	WT-1 vaccine	WT1 HLA class I and II peptides (9-mer modified WT-1 peptide)	Safety (+)		3.5
Fenstermaker et al (2016)[33]	Phase I	N=9, rGBM	SurVaxM	Survivin	Safety, Immunogenicity (+)	2.51	12.4
Crane et al (2013)[34]	Phase I	N=12, rGBM	HSPPC-96 vaccine	Heat shock protein peptide complex (HSPPC-96)	Safety, OS (+)		
Bloch et al (2017)[35]	Phase II, multicenter trial (NCT00905060)	N=46, ND-GBM	HSPPC-96 vaccine	Autologous HSPPC-96	OS (+)	17.8 (95% CI: 11.3–21.6)	23.8 (95% CI: 19.8–30.2)

Ji, n. et al (2018)[36]	Phase I (NCT02122822)	N=20, ND-GBM	HSPPC-96 vaccine	Autologous HSPPC-96	Safety, PFS (+)	11.0 (95% CI: 8.2–13.8)	31.4 (95% CI: 14.9–47.9)
Schijns et al (2015)[37]	Phase I	N=9, rGBM	Gliovac	Autologous antigens (patient' own tissue) plus allogeneic antigens (other glioma patient)	Safety (+)	NA	100% 6-month OS
Liau et al (2005)[38]	Phase I	N=12, GBM	DC-pulsed autologous vaccine	Autologous lysate		19.9	35.8
Prins et al (2011)[39]	Phase I, (NCT00068510)	N=23, rGBM	DC-pulsed autologous vaccine	Autologous lysate	Safety (+)	15.9	31.4 months
Inoges et al (2017)[40]	Phase II, clinical trial (NCT01006044)	N=32 ND-GBM	DC-pulsed autologous vaccine	Autologous lysate	PFS (+)	12.7 (CI 95%: 7–16)	23.4 (95% CI 16–33.1)
Buchroithner et al (2018)[41]	Phase II, multi-center, randomized (NCT01213407)	N=34 ND-GBM	Trivax	Autologous lysate	PFS (-)	28.4% 12-month PFS	564 days, (95% CI: 436–671)
Liau et al (2018)[42]	Phase III, multicenter randomized double-blind trial	N=331 ND-GBM (90% received DCVax®-L)	DCVax®-L	Autologous lysate	PFS (+)	NA	23.1 (95% CI 21.2, 25.4)
Phuphanich et al (2013)[43]	Phase I	N=19 ND- and rGBM HLA-A1(+) and/or -A2(+)	ICT-107	Autologous dendritic cells (DC) pulsed with six synthetic peptide epitopes	Immunogenicity (+)	16.9 (95% CI: 8.9, 49.8)	38.4 (95% CI: 25.9, 40.7)
Wen et al (2019)[44]	Phase II, multicenter randomized double-blind trial (NCT 01280552)	N=81 ND-GBM HLA-A1(+) and/or -A2(+)	ICT-107	Autologous dendritic cells (DC) pulsed with six synthetic peptide epitopes	OS (+)	11.2 (95% CI: 8.22, 13.05)	17.0 (95% CI: 13.6, 20.6)
Rampling et al (2016)[45]	Phase I, clinical trial	N=45 ND-GBM HLA-A*02 positive	IMA950 plus GM-CSF	11 tumor-associated peptides (TUMAPs)	Safety, Tolerability (+)	PFS was 74% at 6 months and 31% at 9 months.	15.3

(*Continued*)

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Table 4 (Continued).

Studies	Trial Phase, Design, NCT	Population Size	Vaccine Type	Antigen Type	Primary Endpoints	Median PFS (Months)	Median OS (Months)
Narita et al (2018)[46]	Phase III, multicenter, randomized, double-blind trial	N=58 HLA-A*24 positive rGBM	Personalized peptide vaccination (PPV)	Four of 12 warehouse peptides (ITK-1) selected based on preexisting peptide-specific IgG levels	OS (-)	NA	8.4 (95% CI: 6.6–10.6)

Abbreviations: NCT, national clinical trial identifier number;; PFS, progression free survival; OS, overall survival; ci, confidence interval; ND-GBM, newly diagnosed glioblastoma; RGBM, recurrent glioblastoma; EGFRvIII, epidermal growth factor receptor variant iii; wt-1, wilm's tumor gene 1; N, number; NA, not available; (+), meeting primary endpoint; (-), failing to meet primary endpoint; HLA-A*02/ HLA-A*24, human leukocyte antigen serotype determined by the antibody recognition of the α2 domain/α^{24} subset of the HLA-A α-chain.

hampered immune responses in patients, as all the patients who needed it for treating side effects were not immune responders. Hence, an in-depth analysis is required to determine the optimum dose of and timing for dexamethasone administration along with chemoimmunotherapy and/or the addition of ICIs. Furthermore, GAPVAC-101 patients received chemoradiotherapy before vaccination, whereas the participants in Keskin et al's study received only radiotherapy. In Keskin et al's trial, all patients were MGMT unmethylated, which is predictive of the clinical benefit from TMZ; hence, chemotherapy was not administered in this trial.[53] GAPVAC-101 included 28.7% of the patients with hypermethylated GBM. There are several other inherent limitations with systematic reviews; for example, the data were derived from different populations and different clinical centers. Population sizes were very small; therefore, efficacy data in the form of PFS and OS should be interpreted with caution.

Conclusion

The results of these trials represent a landmark event in the vaccination paradigm for patients with GBM. Highly personalized vaccines aimed at unmutated and neoantigens have shown greater immunogenicity and safety profiles. Although survival outcomes, particularly those of the GAPVAC-101 trial, were superior to those of previous studies, further larger trials are required to be undertaken to prove treatment superiority in terms of efficacy, as observed with other vaccination strategies in this group of patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

We declare no conflict of interests.

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