Tamavac-TM CLINICAL PROTOCOL

Study Overview

Official Title

Clinical Study on the Therapeutic Efficacy of Nanoparticle Delivered and Personalized Cancer Specific Neoantigenic Peptides conjugated to GBM TAAs, including the MAGE-1, HER-2, gp100, AIM-2, TRP-2, EphA2,105 survivin50, IL13Rα2, heat-shock peptide protein complex-96 (HSPPC-96), and Smac-TLR7/8 peptides, in Patients With Newly Diagnosed Glioma.

Brief Summary

Malignant gliomas are the most common primary brain cancer diagnosed and still carry a poor prognosis despite aggressive multimodal management. Despite the continued advances in immunotherapy for other cancer types, however, there remain no FDA approved immunotherapies for cancers such as glioblastoma. Of the many approaches being explored, cancer vaccine programs are undergoing a renaissance due to the technological advances and personalized nature of their contemporary design. Neoantigen vaccines are a form of immunotherapy involving the use of DNA, mRNA, and proteins derived from non-synonymous mutations identified in patient tumor tissue samples to stimulate tumor-specific T-cell reactivity leading to enhance tumor targeting. In the last several years, the study of neoantigens as a therapeutic target has increased, with the routine workflow implementation of comprehensive next generation sequencing and in silico peptide binding prediction algorithms. Several neoantigen vaccine platforms are being evaluated in clinical trials for malignancies including melanoma, pancreatic cancer, breast cancer, lung cancer, and glioblastoma, among others. Glioblastoma (GBM) remains one of the most challenging cancers to treat. There are approximately 13,000 new cases diagnosed each year with a median survival of less than 15 months, making GBM the most common and fatal primary central nervous system (CNS) cancer in adults. Current treatment typically involves an approach combining maximal safe surgical resection followed by adjuvant radiotherapy and temozolomide chemotherapy. Disease will typically recur and progress within 6–9 months, and there is no gold standard of treatment to prolong survival at time of progression. Unfortunately, despite the seismic influence of immunotherapy on oncology today, there remain no FDA approved immunotherapies for GBM due to the lack of efficacy observed in several randomized clinical trials. There are likely many possible contributors that combine to create an immunologically challenging, or even hostile, environment. GBM is considered to be a particularly striking example of the end result of the cancer immunoediting process, in that a myriad of immunosuppressive features has been described in patients with these cancers including the presence of a significant suppressive myeloid population and even systemic changes leading to T cell sequestration in the bone marrow. In addition, GBM tumors

are considered “non-inflamed” due to the relative paucity of infiltrating T cells. The tumors themselves harbor a low to modest mutational and neoantigen burden compared to other cancer types. Moreover, these tumor-specific antigen targets may be diversely distributed throughout the tumor due to the significant intratumoral molecular heterogeneity observed. We also are gaining an increasing appreciation for the distinct anatomic features that influence the unique immunologic specialization of the CNS, including the meningeal tissues, the presence of spinal fluid, the lack of parenchymal antigen presenting cells, and the recent appreciation of dural lymphatics. More recently, we are also gaining new insights into how neurophysiologic inputs modulate tumor behavior and, potentially, the dynamics of the cancer-immune relationships as well. Thus, there are disease and tissue-specific biological features that create significant challenges for GBM immunotherapy. Despite these unique features, the quest for effective immunotherapies for patients with GBM persists unabated. It is likely that, even in the CNS, immunologic strategies will still need to converge on methods that all must accomplish the same end result: stimulate T cell clonal expansion. Of the immunologic modalities that may achieve this end state, therapeutic cancer vaccines represent a compelling approach that is the subject of this review. Whereas previous experience with cancer vaccines has been limited, there is renewed enthusiasm due to the discovery of tumor-specific targets using powerful genomic tools that allow the generation of vaccines that are truly personalized in nature. Specifically, the term “neoantigen” encompasses a class of tumor-derived antigens derived from the somatic variant proteins that arise in cancer cells but are not present in the host germline. Although many classes of antigens exist in cancer cells, the appeal of neoantigens centers, at least in part, on the immunogenomics-based workflow that is easily and pragmatically integrated into tractable clinical workflows. In this review, we will review in detail the identification of neoantigens, the early experiences targeting these epitopes in clinical vaccine studies, and some of the future directions necessary to accelerate further development of this field. The primary objective of this study is to assess the safety and tolerability, feasibility of the TAMAVAC Vaccines in newly diagnosed glioblastoma (GB) patients using cancer immunogenomics approaches in glioblastoma by exploring the disease-specific issues being addressed in the design of effective personalized cancer vaccine strategies.

Detailed Description

Design Details

METHODS

Trial design and treatment

The trial protocol and all amendments shall be approved by the Interbalkanean Institutional Scientific Board. The trial shall be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and will be registered at ClinicalTrials.gov (https://clinicaltrials.gov/). All patients provided written informed consent before study entry, following DF/HCC IRB protocol approval. All authors attest that the trial shall be conducted in accordance with the protocol and all amendments;

and that they had access to data used for the writing of the manuscript, and vouch for the accuracy and completeness of the data and analyses. Study eligibility shall be assessed among patients seen at the Center for Neuro-Oncology, Dana-Farber Cancer Institute and required: age ≥18 years; Karnofsky performance status ≥70; histopathological confirmation of WHO grade IV glioblastoma (GBM) or variant; tumour MGMT promoter unmethylated by CLIA-certified laboratory; supratentorial tumour with no more than 4 cm in maximal diameter of enhancing tumour on post-operative imaging in any plane; and adequate hepatic, renal and bone marrow function. Patients shall be excluded if: fewer than five actionable neoepitopes were identified for vaccine generation; they developed disease progression following external beam radiotherapy as defined by Response Assessment in Neuro-Oncology (RANO)19; required more than 4 mg of dexamethasone per day within one week before vaccine initiation; developed active infection; or were pregnant or lactating.

SUMMARY

Following surgery, patients will be received conventional radiation therapy administered at 180–200 cGy per fraction daily for five days per week to a total of approximately 60 Gy. Personalized neoantigen vaccines TAMAVAC Vaccine1&2 will be prepared using information from fresh tumour and normal tissue obtained at the time of diagnostic resection, as described below. The vaccine will be administered subcutaneously at least seven to twelve weeks following completion of external beam radiotherapy. TAMAVAC VACCINE1 vaccine will be applied before maintenance TMZ cycles after completion of chemoradiation therapy (CRT). Beginning on day 14 before the first maintenance TMZ cycle, patients from Group A will receive 7 vaccinations with TAMAVAC VACCINE1 drug products during 7 weeks. 900 μg per peptide per vial wiil be used followed by two booster doses eight and sixteen weeks later. For each dose, vaccine pools will be administered within six hours of thawing in a non-rotating fashion to one of up to four extremities. Patients from Group B will be repeatedly vaccinated with TAMAVAC VACCINE2 drug products beginning on day 33 of the 6 maintenance TMZ cycle. Patients will receive 9 vaccinations within 12 weeks. 900-1100 μg per peptide per vial will be used. Concomitant medications deemed necessary for adequate patient care will be allowed, including concomitant corticosteroids for symptoms associated with cerebral oedema, but the study vaccine will be held for patients requiring more than 4 mg per day of dexamethasone within seven days of vaccine administration. Clinical assessment and monitoring will be delivered by using the RANO criteria and the Immunotherapy Response Assessment in the Neuro-Oncology criteria.

Generation of personalized neoantigen vaccines

The personalized neoantigen vaccines will be prepared based on the analysis of whole-exome sequencing (WES) and RNA-seq data generated from fresh-frozen tumours or tumours that will be available as formalin-fixed paraffin-embedded (FFPE) tissue, obtained at the time of diagnostic resection. WES of normal tissue will be generated from autologous PBMC DNA. Details of the WES and RNA-seq protocols wiil be found in the Supplementary Information.

Patient HLA allotype will be assessed using standard class I and class II PCR-based typing (BWH Tissue Typing Laboratory). Coding mutations will be identified and personal neoantigens will be predicted based on binding affinity analysis to individual HLA alleles using the class I MHC binding prediction tool NetMHCpan version 2.422, DeepNeoVX, and SEQ2NEO; with a cut-off of predicted IC50 < 500 nM for selected epitopes.

WES

CLIA-certified WES will be conducted by the Clinical Research Sequencing Platform, Broad Institute WCG eResearch CTMS. Library construction from surgical GBM specimens and matched germline DNA of all patients (Group A&B) will be performed as previously described. For TAMAVAC Vaccine1 treated patients (Group A), whole-exome capture was performed using the Agilent SureSelect Human All Exon 44 Mb version 2.0 bait set (Agilent Technologies). For TAMAVAC Vaccine2 treated patients (Group B) WES will be performed using the Illumina Nextera Rapid Capture Exome version 1.2 bait set. Data will be analysed using the Broad Picard Pipeline (version 1.752), which includes de-multiplexing, duplicate marking and data aggregation.

RNA-seq.

For RNA-seq library construction, RNA will be extracted from fresh-frozen sections or FFPE samples using the Qiagen AllPrep DNA/RNA/miRNA Universal Kit or Qiagen AllPrep DNA/RNA FFPE Kit, respectively. RNA-seq libraries will be prepared using Illumina TruSeq Stranded mRNA Library Prep Kit or Illumina's TruSeq RNA Access Library Prep Kit (Supplementary Table 1b). Total RNA will be quantified using the Quant-iT RiboGreen RNA Assay Kit and normalized to 5 ng μl−1. For TAMAVAC Vaccine1&2 treated patients (Group A&B), each sample will be transferred into a library preparation which is an automated variant of the Illumina TruSeq Stranded mRNA Sample Preparation Kit. The resulting libraries will be quantified with qPCR using the KAPA Library Quantification Kit for Illumina Sequencing Platforms. Data will be analysed using the Broad Picard Pipeline, that includes de-multiplexing and data aggregation. RNA-seq data will not available for patients with tissue necrosis in the tumour sample.

DNA quality control

Broad Institute protocols as previously described, will be used for DNA quality control. The identities of all tumour and normal DNA samples will be confirmed by fingerprint genotyping of 95 common single-nucleotide polymorphisms by Fluidigm Genotyping (Fluidigm). Sample contamination by foreign DNA will be assessed using ContEst (version 1.4).

Somatic mutation calling

Somatic mutations will be identified by Clinical Laboratory Improvement Amendments (CLIA)-certified whole-exome sequencing of DNA from surgically resected glioblastoma and matched normal cells (PBMCs) and their expression will be confirmed by tumour RNA-seq. Immunizing peptides will be selected based on HLA class I binding predictions (Methods). Beginning on day 14 before the first maintenance TMZ cycle, patients will receive 7 vaccinations with TAMAVAC VACCINE1 drug products during 7 weeks, 900 µg per peptide per vial will be used before maintenance TMZ cycles after completion of chemoradiation therapy (CRT). Patients which will be repeatedly vaccinated with TAMAVAC VACCINE2 drug products beginning on day 33 of the 6 maintenance TMZ cycle will receive 9 vaccinations within 12 weeks. 900-1100 µg per peptide per vial will be used. Analyses of WES data of tumour and matched PBMCs (as source of normal germline DNA) from the all the patients (Group A&B) will be used to identify the specific coding-sequence mutations, including single-, di- or tri-nucleotide variants that lead to single amino acid missense mutations and small insertions/deletions (indels). Output from Illumina software will be processed by the Broad Picard Pipeline to yield BAM files, which contained aligned reads (bwa version 0.5.9, aligned to the NCBI Human Reference Genome Build hg19) with well-calibrated quality scores. Somatic alterations will be identified using a set of tools within the 'Firehose' pipeline (https://software.broadinstitute.org/cancer/cga/). Somatic single nucleotide variations (sSNVs) will be detected using MuTect (Firehose version 13112); somatic small insertions and deletions will be detected using Indelocator (version 1.0)25 and Strelka (version 1.0.11). All indels will be manually reviewed using the Integrative Genomics Viewer (IGV version 2.4). All somatic mutations, insertions and deletions will be annotated using Oncotator (version 1.4.1). The ABSOLUTE algorithm (version 1.1) will be used to calculate the purity and ploidy of the samples. RNA-seq data will be processed using the PRADA software (version 1.1)32 and tumour transcriptional data will be displayed alongside data from normal brain cortical tissue from the GTEx project (analysis V6, dbGaP accession phs000424.v6.p1) and from GBM from TCGA.

Identification of target epitopes for TAMAVAC Vaccine1&2 design.

NetMHCpan version 2.4, DeppNeoVX, and SEQ2NEO shall be used to identify mutation-containing epitopes that shall be predicted to bind to the MHC class I molecules of each individual patient. Up to17-25 (LIMPs, ASPs, and bEPTs) peptides in average of 7-13 AAs each from patients own derived somatic mutants arose from up to 30 independent mutations shall be selected and prioritized for peptide preparation. Mutations in oncogenes shall be given the highest priority within each ranked group. Only sSNVs that demonstrated expression of the mutated allele shall be used. Additionally, a variety of possible biochemical properties (hydrophobicity or presence of multiple cysteines), which may affect the synthesizability or solubility of the long peptide shall be considered.

Synthesis of TAMAVAC VACCINES 1&2, pooling and final vaccine preparation.

Good Manufacturing Practice (GMP) (LIMPs, ASPs, and bEPTs) peptides 17–25 amino acids in length will be synthesized by standard solid-phase synthetic peptide chemistry and purified using reverse phase high performance liquid chromatography (RP-HPLC) (CSBio). Each one of our TAMAVAC VACCINE1 is consisted of 17-35 (LIMPs, ASPs, and bEPTs) Personalised Synthetic Neoantigenic Peptides conjugated to GBM TAAs, including MAGE-1, HER-2, gp100, AIM-2, TRP-2, EphA2,105 survivin50, IL13Rα2, heat-shock peptide protein complex-96 (HSPPC-96), and Smac-TLR7/8 peptides. TAMAVAC VACCINE1 drug products are composed of 17-25 peptides from the Biogenea Pharmaceuticals Ltd warehouse. cGAMP, Granulocyte-macrophage colony stimulating factor (GM-CSF), polyinosinic–polycytidylic acid with polylysine and carboxymethylcellulose (Poly-ICLC), imiquimod, CpG oligodeoxynucleotides, saponins and monophosphoryl lipid A (MPLA)（500ug）will be used as immunomodulators with all vaccinations. The TAMAVAC Vaccine2 is consisted of cGAMP, Granulocyte-macrophage colony stimulating factor (GM-CSF), polyinosinic–polycytidylic acid with polylysine and carboxymethylcellulose (Poly-ICLC), imiquimod, CpG oligodeoxynucleotides, saponins and monophosphoryl lipid A (MPLA) that are conjugated to GBM TAAs, including MAGE-1, HER-2, gp100, AIM-2, TRP-2, EphA2,105 survivin50, IL13Rα2, heat-shock peptide protein complex-96 (HSPPC-96), and Smac-TLR7/8 peptides and self-assembled into nanoparticles around 20 nm in size. The peptide antigens are complexed with personalized neoantigens and are linked to a hydrophobic block on end to facilitate particle formulation through micellization into the nanocarrier and to increased peptide antigen immunogenicity. A charge-modifying group is incorporated on the opposite end to stabilize the nanoparticles (~20 nm in size). The TAMAVAC Vaccine2 is a combined neoepitope cancer specific vaccine and is (Tetanus Toxoid, Poly-ICLC, GM-CSF, Imiquimod, Immune Checkpoint inhibitors) accompanied and consisted of 17-25 (LIMPs, ASPs, and bEPTs) in average of 7-13 AAs each from patients own derived somatic mutants and reported GBM antigens for the first and second vaccination to effectively stimulate antigen-specific CD4+ and CD8+ T cells in 17 to 21 weeks with an excellent safety profile. The TAMAVAC Vaccine2 contains basic epitope peptides (bEPTs) of 8 to 9 sequenced amino acids that bind to personal human leukocyte antigen (HLA) alleles, identified by using class I binding predictive algorithms, up to 20 minimal class I epitope peptides which were chosen as neoantigen vaccine targets, and are included within synthetic long immunizing peptides (LIMPs) of 17 to 25 sequenced amino acids. The TAMAVAC Vaccine2 is administered to the GBM patients as immunizing peptides; they are synthetized by a commercial peptide vendor, cleaved and purified under good manufacturing practice (GMP) conditions. The TAMAVAC Vaccine2 long peptides, LIMPs are synthesised for vaccine administration to effectively stimulate antigen-specific CD4+ and CD8+ T cells. The TAMAVAC VACCINE2 will be ready for use 1 month after enrollment, as these peptides have to be newly synthesized for each patient following identification of the mutanome and corresponding mutated peptides in the HLA ligandome. TAMAVAC VACCINE2 drug products are composed 17-25 peptides de novo synthesized for an individual patient.

Clinical event timeline and Dosing of TAMAVAC VACCINES 1&2

Clinical event timeline for the patients who received at least one vaccine dose of TAMAVAC VACCINE1&2, will be calculated from surgery until time of death due to progressive disease. Median progression-free survival (PFS) and overall survival (OS) will be also calculated respectively. Among enrolled patients, a median of (110-145) somatic single-nucleotide variants per tumour (range, 75–158) will be tested with a median of (58-63) coding mutations per tumour (range, 32–93) using whole-exome sequencing, and the expression of a subset of genes will be confirmed by RNA sequencing (RNA-seq) analysis. These included mutations commonly observed in glioblastoma that affect PTEN, RB1 and EGFR. No IDH1 or IDH2 mutations will be also tested. A median of 60.5-70,8 HLA binders (range, 30–163) with a half-maximum inhibitory concentration (IC50) < 500 nM will be predicted per tumour. Five to six patients are expected to be withdrawn because of an insufficient number of actionable neoepitopes or disease progression after radiotherapy. For the remaining patients, the median number and amino acid length of peptides incorporated per vaccine will be 17-25 (LIMPs, ASPs, and bEPTs) in average of 7-13 AAs each from patients own derived somatic mutants 12 (range, 7–20) and 24 (range, 15–30), respectively. Median time from surgery to first vaccination will be 19.9 weeks (range, 17.1–24.7 weeks).

Processing of GBM and PBMC specimens for scRNA-seq

Surgically resected GBM tissue from patients from both Groups A&B vaccinated with TAMAVAC VACCINE1&2 vaccine Drugs will be obtained on ice within 30 min of lesion excision. The tumour specimen will be mechanically disrupted into small pieces with a disposable, sterile scalpel and further dissociated into a single-cell suspension using the enzymatic brain dissociation kit (P) from Miltenyi Biotec, following the manufacturer's protocol. Fc receptor blocking will be performed on the total cell suspension using Human TruStain FcX (Biolegend). The cell suspension will be subsequently stained for flow cytometry using antibodies against CD45 [HI30]-BV605, CD3 [HIT3a]-BV510 from BD Bioscience, CD4 [OKT4]-PE–Cy7, CD8 [HIT8a]-PerCP–Cy5.5, exclusion panel–APC (CD14 [63D3], CD64 [10.1], CD163 [GHI/61], CD15 [HI98] from Biolegend and CD66b [G10F5] from ThermoFisher Scientific). The tumour cell suspension will be next spiked with 1 µM calcein AM (ThermoFisher) to enable gating of live cells and incubated in the dark at room temperature for 10 min. Live, single T cells (gating: calcein AM+, exclusion−, CD45+, CD3+, CD8+ or CD4+) will be sorted into individual wells of a 96-well twin.tec PCR plate (Eppendorf), which contained 10 µl per well of RLT buffer (Qiagen), using an AriaIII fluorescence-activated cell sorter (FACS) with a 70-µm nozzle (BD Biosciences). Plates will be immediately centrifuged at 800g for 1 min at 4 °C and frozen on dry ice. Single neoantigen-reactive CD4+ and CD8+ T cells will be isolated from PBMCs of patient 7, obtained 8–16 weeks after vaccine initiation. For isolation of CD4+ T cells, PBMCs will be stimulated in vitro with 10 µg ml−1 of ASP peptide pools overnight, and then subsequently flow cytometrically be sorted on the basis of IFNγ secretion (IFNγ Secretion Assay, Miltenyi Biotec) and co-expression of CD3+ and CD4+ into 96-well plates (FACSAria II Cell Sorter, BD Biosciences). Single neoantigen-reactive CD8+ T cells will be isolated from PBMCs from patients from both Groups A&B vaccinated with TAMAVAC VACCINE1&2 vaccine Drugs which

will be stimulated with 10 μg ml−1 of EPT peptides, corresponding to the ARHGAP35MUT or SLX4MUT peptides in DMEM complete medium supplemented with 10% human serum. Three days after stimulation, the cells will be supplemented with human IL-2 (20 units) and human IL-7 (20 ng ml−1). The medium will be replenished as necessary over three weeks of culture, after which CD8+ T cells will be enriched (CD8 magnetic beads, Miltenyi Biotec), rested overnight in cytokine-free medium and then stimulated overnight with autologous APCs (CD4- and CD8-depleted PBMCs) loaded with peptide (10 μg). Subsequently, IFNγ-producing neoantigen-responsive cells will be stained and sorted as single cells into 96-well plates, as above.

Circulating immune responses to immunizing peptides (IMPs)

Circulating immune responses to immunizing peptides (IMPs) will be analysed among the patients who received at least one TAMAVAC VACCINE1&2. Peripheral blood mononuclear cells (PBMCs) will be tested for reactivity against pools of overlapping 15- to 16-amino acid peptides (assay peptides (ASPs)) corresponding to the immunizing peptides. All dexamethasone TAMAVAC VACCINE1&2 treated patients who required during TAMAVAC VACCINE1&2 priming will be tested for interferon-γ (IFNγ) responses. Diffuse early reactivity from patients treated with dexamethasone TAMAVAC VACCINE2 vaccinated probably will reflect high baseline inflammation that subsequently dissipated. By contrast, TAMAVAC VACCINE1 patients who did not receive dexamethasone during vaccine priming, they may generate robust de novo immune responses against multiple predicted neoantigens as will be analyzed using ex vivo enzyme-linked immunospot assays(ELISPOT). TAMAVAC VACCINE2 vaccinated patients who has been responded primarily to pool C peptides, they will be assessed to CD4+ T cell responses against mutated ARHGAP35 and GPC1 neoepitopes, and preferential reactivity to mutant over wild-type peptides. Mutant-specific CD8+ T cell responses to predicted class I epitopes (EPT) that arose from mutated ARHGAP35 (ARHGAP35MUT) and mutated SLX4 (SLX4MUT) will be assessed following one round of in vitro stimulation in TAMAVAC VACCINE2 post-vaccination patients. Preferential targeting of mutant SHANK2 (SHANK2MUT) and SVEP1 (SVEP1MUT) over wild-type sequences and equivalent reactivity of mutant versus wild-type COX18 will be tested in both TAMAVAC VACCINE1&2 group of patients. The strongest neoantigen-specific responses from both TAMAVAC VACCINE1&2 group of patients will be confirmed to be against processed epitopes.

Conclusions

In conclusion, TAMAVAC VACCINE1&2 neoantigenic vaccinations will be evaluated as a feasible therapeutic strategy for immunologically cold tumours with a relatively low mutational burden with an aim to decrease the number of CD4+ T cells which have been reported in glioblastoma tumours that relapse rapidly, showing that low levels of infiltrating T cells at diagnosis increased only among patients who generated neoepitope-specific systemic immune responses. Furthermore, a subset of these T cells will be isolated within resected intracranial glioblastoma tumours which is specific for neoantigens targeted by

vaccination. While the reasons for this are unknown, similar findings were observed in melanoma personal neoantigen vaccine trial using RNA-encoding MHC class I predicted binding epitopes. Optimization of algorithms that predict the immunogenicity of CD8+ epitopes, and eventually CD4+ epitopes, may help to clarify these results as well as enhance immunogenicity. That will be a signelcenter, open-label, single arm, first-in-human phase I trial to investigate the safety, feasibility and immune response of the novel TAMAVAC Vaccine in patients with newly diagnosed GB. TAMAVAC-TM clinical protocol shall be focusing on the prediction and the designing of Cancer Specific Neoantigens from patien's own somatic mutations that differ from wild-type antigens and shall be specific to each individual patient providing tumor specific targets for developing personalized cancer vaccines.

Primary Endpoints:

Determine the safety and tolerability profile of TAMAVAC Vaccine1 and 2 when co-administered with immunomodulators and Stupp standard treatment.

Secondry Endpoints:

Descriptive analysshall be of induced T-cell immune responses after vaccinations with TAMAVAC Vaccine1and 2 drug products plus immunomodulators and Stupp standard treatment.

Overall survival with TAMAVAC Vaccine1 and 2 plus immunomodulator in newly diagnosed glioma in patients treated with standard Stupp.

Progression-free survival with TAMAVAC Vaccine1 and 2 plus immunomodulator in newly diagnosed glioma in patients treated with standard Stupp.

After the standard chemoradiotherapy with TMZ has been completed, Vaccination shall be initiated 14 days before the first maintenanceTMZ cycle. It starts with the first Group of Patients (Group A) vaccinated by the TAMAVAC Vaccine1, followed by additional Group of Patients (Group B) treated by the TAMAVAC Vaccine2 at the same time point and ends with the Last Endpoint and Comparative Evaluation Studies between the patients.

Primary Purpose : Treatment

Allocation : N/A

Interventional Model : Single Group Assignment

Masking : None (Open Label)

Arms and Interventions

What shall be the study measuring?

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
Safety and toleration	Determine the safety and tolerability profile of TAMAVAC Vaccine1and 2 when administered adminshall betered with immunomodulators and Stupp standard treatment	Continously for about 40 weeks plus follow-up

Secondary Outcome Measures

Outcome Measure	Measure Description	Time Frame
T-cell immune response	Descriptive analysis of the induced T-cell immune responses after vaccinations with TAMAVAC Vaccine1and 2 drug products plus immunomodulators and Stupp standard treatment.	till 24 months of vaccination
Overall survival(OS)	Overall survival with TAMAVAC Vaccine1 and 2 plus immunomodulator in newly diagnosed glioma in patients treated with standard Stupp.	till 24 months of vaccination
Progression-free survival （PFS）	Progression-free survival with TAMAVAC Vaccine1 and 2 plus immunomodulator in newly diagnosed glioma in patients treated with standard Stupp.	till 12 months of vaccination

Collaborators and Investigators

Sponsor

-Interbalkanean Medical Center

Collaborators

-Biogenea Pharmaceuticals Ltd

Investigators

-Principal Investigator: Professor Emmanouelides