H3 K27M-altered Glioma and Diffuse Intrinsic Pontine Glioma: Semi-systematic Review of Treatment Landscape and Future Directions

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Abstract

H3 K27M-mutant diffuse glioma is a recently identified brain tumor associated with poor prognosis. As of 2016, it is classified by the World Health Organization as a distinct form of grade IV glioma. Despite recognition as an important prognostic and diagnostic feature in diffuse glioma, radiation remains the sole standard of care and no effective systemic therapies are available for H3K27M mutant tumors. This review will detail treatment interventions applied to diffuse midline glioma (DMG) and diffuse intrinsic pontine glioma (DIPG) prior to the identification of the H3 K27M mutation, the current standard-of-care for H3 K27M-mutant diffuse glioma treatment, and ongoing clinical trials listed on www.clinicaltrials.gov evaluating novel therapeutics in this population. Current clinical trials were identified using clinicaltrials.gov, and studies qualifying for this analysis were active or ongoing interventional trials that evaluated a therapy in at least one treatment arm or cohort comprised exclusively of patients with DIPG and H3 K27M-mutant glioma. Forty-one studies met these criteria, including trials evaluating H3 K27M vaccination, chimeric antigen-receptor T cell therapy, and small molecule inhibitors. Ongoing evaluation of novel therapeutics is necessary to identify safe and effective interventions in this underserved patient population.

Keywords: H3 K27M, H3 K27-altered, clinical trials, diffuse midline glioma, diffuse intrinsic pontine glioma

Key points

- H3 K27M-mutant diffuse glioma, including DIPG, has a poor prognosis and no effective treatments; there is a significant unmet need for effective therapies.
- A variety of novel investigational approaches are now being explored for DIPG.

Importance of Study

This comprehensive review provides an up-to-date account of ongoing clinical trials for the treatment of H3K27M-mutant and Diffuse Intrinsic Pontine Glioma. As such, this work can guide current management and future studies for improved clinical care of patients with this disease.

Introduction

The presence of the H3 K27M mutation is an important diagnostic feature in diffuse midline glioma (DMG), which can occur in the thalamus, pons, cerebellum, or spinal cord, and includes diffuse intrinsic pontine glioma (DIPG). In these tumors, with a median overall survival of 10.1 to 14.4 months from diagnosis, its presence is associated with inferior prognosis compared to patients with H3 wild-type tumors.[1,2] The 2021 World Health Organization (WHO) central nervous system (CNS) classification criteria defines H3 K27-altered DMG as a separate category of high-grade glioma (HGG), regardless of histological features.[3] However, prior to identification of the mutation, biopsy was not commonly performed due to the risk associated with surgical intervention, especially in the brainstem. As a result, the existence of molecularly and/or morphologically distinct subsets of DMG and pediatric DIPGs was not fully appreciated.[4] Before the significance of the H3 K27M mutation in subsets of DMG and DIPG was understood, multiple treatments including various chemotherapy regimens that previously demonstrated efficacy in adult glioma patients were investigated in these patients; however, no significant improvement in survival was demonstrated. This review will focus on treatments for H3 K27M-mutant glioma and DIPG, including a brief review of therapies that were evaluated prior to identification of this alteration.

Historical Treatment Approaches for DMG and DIPG

In this narrative portion of the review, we highlight notable publications that helped define the historical strategy for DMG and DIPG treatment. Therefore this section, while not intended to be exhaustive, is meant to present the historical approaches to DMG and DIPG management in order to provide context for understanding the current treatment landscape and advances in the treatment of DMG and DIPG over the past decade that follows.

Radiation therapy is a key component of the treatment of glioma, with a standard dose of 54-60 Gy that temporary alleviates symptoms.[5] Prior to the identification of the H3 K27M mutation, various radiation schedules were attempted in an effort to optimize efficacy in these patients, with little gain in survival. In pediatric patients with newly diagnosed DIPG, hypofractionated radiotherapy, delivered at 13 fractions of 3 Gy or six fractions of 5.5 Gy over three weeks, resulted in a median OS of only 8.6 months[6]; similarly, another study in DIPG found that a total dose of 45 Gy, delivered as daily 3 Gy for 3 weeks, had a median overall survival (OS) of 7.6 months.[7] Re-irradiation has been administered to patients with progressive disease. For example, in a retrospective chart review of 26 patients, a schedule of 20 Gy in 10 daily fractions of intensity-modulated radiation therapy was administered in patients with DIPG undergoing re-irradiation, which was well tolerated without observed treatment toxicity.[8] A separate phase 1/2 study of 12 patients evaluated three dose levels in patients with DIPG undergoing re-irradiation and determined that a course of 24 Gy in 12 fractions was the most appropriate regimen.[9] Importantly, a Canadian study demonstrated safety and feasibility of re-irradiation in 16 DIPG patients, with neurological improvement observed in all but three.[10]

Various chemotherapy schedules and combinations were assessed for efficacy in patients with DMG and DIPG, following or in combination with radiotherapy, largely without encouraging results. A regimen including cisplatin, etoposide, vincristine, and combination cisplatin, etoposide, and ifosfamide, provided no improvement in OS in pediatric patients with pontine tumors (n=37) or lesions outside the pons with residual tumor following resection, relative to historical controls.[11] Another trial assessed neo-adjuvant frontline chemotherapy (alternating carmustine and methotrexate cycles) in 23 pediatric patients with diffuse brainstem tumors who had progressed after chemotherapy; while median OS in this molecularly unselected population of patients was 17 months, the 3-year OS rate was only 4% and treatment was associated with serious complications such as septicemia, which required hospitalization.[12] Furthermore, in 63 patients with newly diagnosed DIPG, combined chemo-irradiation with temozolomide, also failed to improve OS

compared to older regimen (one-year OS 40%).[13] Similar single arm studies on pediatric populations with DIPG also showed no evidence of improved survival with combined radiotherapy and temozolomide, compared to historical controls.[14,15]

A variety of targeted therapies were also attempted in pediatric glioma patients; however, clinically meaningful improvements were not observed in those with brainstem gliomas. Tipifarnib, a farnesyltransferase inhibitor, given concurrent with radiotherapy achieved a 1-year OS rate of 36.4% (SE 16.7%) in pediatric patients with newly diagnosed diffuse brainstem glioma, compared to a historical control of 30.0%±3%.[16] The tyrosine kinase inhibitor (TKI) imatinib together with radiotherapy achieved a 1-year event free survival of 45.0% ±11.1% in newly diagnosed pediatric patients with DIPG, however, treatment was associated with an increased risk of intratumoral hemmorage.[17] The EGFR inhibitors gefitinib and erlotinib were also associated with intratumoral hemorrhage; median OS with gefitinib in pediatric patients with newly diagnosed brain stem glioma or incompletely resected supratentorial malignant glioma was 4.1-12 months, depending on dose level.[18,19] Vandetanib, a VEGFR inhibitor, given concurrent with radiotherapy, achieved 1- and 2-year OS rates of 37.5% and 21.4%, respectively, in pediatric patients with newly diagnosed DIPG.[20] Lastly, a phase II clinical trial was conducted examining nimotuzumab and radiotherapy for treatment of newly diagnosed DIPG.[21] In this trial, concomitant treatment with RT and nimotuzumab was found to be feasible in an outpatient setting, with comparable PFS and OS to RT and intensive chemotherapy in hospitalized setting.

Convection enhanced delivery (CED) is a technique designed to enhance the availability of targeted therapies within the brain, as both the blood-brain barrier (BBB) and the midline location of tumors such as DIPG may present obstacles to achieving therapeutic concentrations within the tumor.[22] When administered via CED, a treatment is delivered via catheters to interstitial areas of the brain, thereby providing the treatment to an extracellular space more proximal to the tumor.[23] While still experimental, this technique was recently evaluated in seven pediatric patients with DIPG

following radiation, in which the anti-CD276 antibody ^{124}I-omburtamab was administered into the brainstem using CED. The treatment was generally well tolerated, with no grade 3 or higher adverse events observed, and was considered feasible by the investigators.[24] Future research, including ongoing phase 1 trials of ^{131}I-omburtama[25] and a gold nanoparticle formulation of the histone deacetylase (HDAC) inhibitor panobinostat[26] delivered using CED, will help determine the efficacy of CED in the treatment of midline tumors.

Identification of H3 K27M Mutation Defines A Disease

H3 K27M-mutant glioma is a recently identified entity. The discovery of the somatic H3 K27M mutation was reported in two independent publications in 2012, using exome sequencing of pediatric glioblastomas[27] and whole-genome sequencing of DIPG samples.[28] Subsequent studies have demonstrated that the H3 K27M mutation may occur in H3.1 or H3.3 isoforms of the protein, and is generally a founder mutation that is retained throughout the course of the disease and throughout the tumor, though occasional mosaic immunostaining throughout a tumor has been reported in case studies.[29-31] While the presence of H3 K27M mutation co-occurs with many other genetic alterations (for example, H3.3 with p53 mutation and H3.1 with ACVR1)[32-35] it is mutually exclusive with IDH and EGFR mutations.[36] Studies have shown that K27M-mutant tumors are almost always MGMT promoter unmethylated, explaining the lack of benefit observed when temozolomide was added to radiotherapy for DIPG treatment.[13] Importantly, H3 K27M-mutant tumors are notable for a global loss of H3 K27 trimethylation and an attendant gain of H3K27Ac (acetylation), rendering silencing of tumor suppressor genes and activation of tumor oncogenes.[37] This loss of H3K27me3 is also incorporated into current neuropathological assessments of biopsies using immunohistochemistry.

Further underscoring the appreciation of this alteration as a disease-defining mutation, the 2016 World Health Organization (WHO) classification of central nervous system tumors subsequently categorized H3 K27M-mutant DMG as a distinct form of Grade IV glioma, regardless of

other histological features. In the 2021 update to this classification, the WHO refined this classification as H3 K27-altered, due to recognition of other pathways which may also underly the pathogenesis of these tumors.[3]

The presence of the H3 K27M mutation is associated with dismal survival, although the reported prognostic magnitude relative to gliomas without the H3 K27M mutation depends on many variables.[38-43] While the H3 K27M mutation was discovered in DIPG and is often thought to be a pediatric disease, young adult patients are also affected. Reports indicate up to 90% of pediatric DIPG cases are H3 K27M-mutant. Among adults with DMG, the H3 K27M mutation occurs in 15-60% of cases. In a study of young adult and adult patients with thalamic tumors, the mutation was absent in all patients over the age of 50, whereas 91% of patients under the age of 50 (range, 17-46 years) were H3 K27M-mutant.[44]

Current Standard of Care for H3 K27M glioma

At present, standard of care for patients with H3 K27M disease is radiation (total, 54-60 Gy; 2 Gy per daily fraction over 6 weeks); in patients with DIPG, 54 Gy is usually given due to the lower radiation tolerance of the brainstem.[5,40] This is the only treatment which has shown even a modest effect on survival. Given the unique biology of H3 K27M-mutant gliomas, its poor prognosis, the absence of effective systemic treatments, and the historical lack of success in applying previously developed intervention to this population, the need for new therapeutic approaches for this disease remains high.

Clinical Trials Currently Assessing Potential Therapies for H3 K27M-mutant Glioma

To identify current treatments being tested in H3 K27M-mutant glioma and DIPG, several searches were conducted on clinicaltrials.gov on July 18th, 2023, with results limited to interventional studies that were not yet recruiting or recruiting. Searches were conducted using the following terms for Condition or Disease: DIPG, K27-altered, or K27M. Results for expanded access protocols

were included where available. Following de-duplication, 57 unique trials remained. Fourteen of these trials were excluded due as they did not include analysis of K27M-mutant diffuse glioma or DIPG separately from other qualifying tumors (e.g., solid tumors, all gliomas, etc). An additional two studies were excluded, as K27M-mutant disease was excluded (n=1) or because the subject of the study was a stratification method, rather than a treatment (n=1). The remaining 41 studies were included in this review (**Supplementary Figure 1; Supplementary Table 1**).

Chemotherapy

Historically, efforts to treat DIPG with chemotherapy have proven unsuccessful, despite over 45 years of clinical trials of a wide variety of agents and regimens.[45] This could be due to the fact that many chemotherapeutic agents do not cross the blood brain barrier into tumor tissue in sufficient concentration. Two active chemotherapy trials were identified for treatment of DIPG. The first is a single site, open label, early Phase 1 study of gemcitabine (**Table 1,** NCT02992015).[46] Patients aged 3-17 years may participate in this study if newly diagnosed (radiographic or histologic) with DIPG. All patients on-study receive 2100 mg/m2 IV gemcitabine over 30 minutes, within 4 hours of planned tumor biopsy. PK testing for levels of gemcitabine, its metabolite difluorodeoxyuridine (dFdU), and gemcitabine nucleotides in peripheral blood and DIPG tumor tissue will be performed using LC-MS/MS, in order to determine if gemcitabine is able to cross the blood brain barrier.

A second novel chemotherapy study is designed to investigate the efficacy of pomalidomide monotherapy as a treatment for recurrent or progressive DIPG or HGG (**Table 1,** NCT03257631).[47] Pomalidomide is an immunotherapeutic agent known to enhance T cell- and natural killer cell-mediated immunity.[48] It also inhibits production of proinflammatory cytokines, such as TNF-α and IL-6, by monocytes, and has antiangiogenic properties.[48] In this multi-site, open label Phase 2 trial, patients 1-21 years of age will be treated with oral pomalidomide, where objective response rate (ORR) and long-term stable disease rate will be measured as primary outcomes.

Re-irradiation

Fractionated radiation of approximately 60 Gy is the mainstay of DIPG therapy. However, while this may provide relief of symptoms for approximately six months. A Canadian consortium is currently investigating the efficacy of re-irradiation for patients of any age with progressive or recurrent DIPG (**Table 1,** NCT03126266).[49] Patients may qualify for this multi-site study if they have evidence of progression or recurrence after receiving a cumulative radiation dose of ≥60 Gy at least 180 days prior to re-irradiation. Participants receive 30.6 Gy or 36 Gy as a second course of radiation therapy, and are evaluated for second PFS as the primary outcome measure, with OS as a secondary outcome measure.

Vaccination

H3K27M Vaccines

Midline gliomas are often characterized as immunologically cold due to the absence of tumor-infiltrating lymphocytes (TILs). This is reflected by immune-oncology (IO) agents so far having failed to demonstrate efficacy in this disease.[50] In an effort to transform the tumor micro-environment (TME) into an immunologically hot state, in which immune cells detect and kill cancer cells, vaccines utilizing tumor antigens are being evaluated in many forms of cancer to determine if they can engender a tumor-specific immune response. Three early phase clinical trials were identified on clinicaltrials.gov that are evaluating vaccination in patients with H3 K27M-mutant disease. One additional study is designed to examine the efficacy of a novel peptide vaccine in treating newly diagnosed pediatric HGG and DIPG, while a final study investigates a neo-epitope vaccine for the treatment of newly diagnosed DMG and DIPG.

A synthetic H3 K27M peptide (H3.3K27M$_{26–35}$) was identified as a potential binder to HLA-A*0201 using MHC-binding algorithms. In murine models, this peptide induced a mutation-specific immune response, including both cytotoxic and T-helper-1-cell mediated immune responses.[51] In a

murine xenograft model of glioma, adoptively transferred CD8+ T-cells transduced with a H3.3K27M$_{26–35}$-specific T-cell receptor resulted in a significant delay in disease progression.[52] To evaluate the feasibility and efficacy of vaccination with the K27M synthetic peptide in patients, a Phase 1/2 peptide vaccine trial with polyIC ± nivolumab is currently underway in pediatric patients with newly diagnosed H3 K27M-mutant DIPG or non-pontine DMG (**Table 1,** NCT02960230); as this vaccine targets an human leukocyte antigen (HLA)-restricted epitope, all patients must be HLA-A2 (02:01)+. In their publication on this ongoing trial, Mueller, et al. (2020) reported that among 18 patients with DIPG and available data, six demonstrated a H3 K27M-reactive immune response. The vaccine was well tolerated; the most common treatment-related adverse event (TRAE) was injection site reaction.[53]

Also utilizing a synthetic H3.3K27M peptide vaccine, the phase 1 trial INTERCEPT H3 trial is designed to evaluate the H3 K27M vaccine in combination with radiotherapy and the anti-PD-L1 antibody atezolizumab in adults with H3 K27M-mutant DMG (**Table 1**; NCT04808245). Immune checkpoint inhibitors are antibody therapeutics which prevent inhibition of T-cell proliferation, potentially boosting immune responses against tumor cells, thereby amplifying immune-mediated anti-cancer effects resulting from the cancer vaccine. Atezolizumab, an anti-PD-L1 monoclonal antibody, has previously demonstrated safety in adults with glioblastoma; however, small trials failed to give evidence of clinical activity. This phase 1 trial will evaluate the efficacy of 11 doses of the H3 K27M vaccine in patients receiving standard radiation followed by a course of atezolizumab delivered once every three weeks. The primary endpoints include safety and assessment of immunogenicity. This study is currently open and enrolling patients.

ENACTING, a phase 1 study of the H3.3-K27M targeted neoantigen peptide in combination with standard-of-care radiotherapy, is being conducted in pediatric and adult patients with H3 K27M-mutant DIPG with the HLA-A2 subtype (**Table 1,** NCT04749641). The primary objectives are safety and 1-year OS rate. This trial is currently enrolling patients.

Importantly, other research groups have failed to demonstrate that vaccination results in endogenous processing and presentation of the H3 K27M epitope by cancer cells. With these early phase clinical trials ongoing, the role of vaccination in H3 K27M-mutant disease will be better understood in due time.

PEP-CMV Vaccine

A multi-center Phase II study is being conducted to determine the efficacy of a novel peptide vaccine, PEP-CMV, which targets CMV antigen in the treatment of patents aged 3-25 years with newly diagnosed pediatric HGG and DIPG (**Table 1,** NCT05096481).[54] In this study, patients must enroll within 6 weeks of their final dose of standard of care radiation therapy (required for DIPG patients), with or without chemotherapy. Participants will receive standard chemotherapy with temozolomide for five days, followed by the study vaccine, intradermal PEP-CMV on day 21. The primary outcome measure is 1-year OS for both HGG and DIPG.

Neo-epitopes

rHSC-DIPGVax is a neo-antigen heat shock protein containing 16 peptides reflecting neo-epitopes found in the majority of DIPG and DMG tumors. A multi-center trial testing vaccination targeting these neo-epitopes in pediatric DMG and DIPG is currently recruiting (**Table 1**, NCT04943848). This study is a phase I clinical trial evaluating the safety and tolerability of rHSC-DIPGVax in combination with Balstilimab and Zalifrelimab (immune checkpoint inhibitors). Newly diagnosed patients with DIPG and DMG who have completed radiation six to ten weeks prior to enrollment are eligible for this study.

Adoptive Transfer

Chimeric Antigen Receptor T-cell Therapy

Chimeric antigen receptor T-cell (CAR-T) therapy is a treatment that entails isolating autologous T cells from patient's blood and transducing them to express a T-cell receptor (TCR) specific for a cancer-associated antigen. When these CAR-T cells are reintroduced to the patient's system, these antigen-specific T cells help steer anti-cancer immune responses, potentially resulting in the clearance of cancer cells while leaving healthy cells intact. Currently approved CAR-T therapies are limited to B-cell malignancies; however, ongoing work is evaluating application of CAR-T therapy in patients with solid tumors.[55] On clinicaltrials.gov, three phase 1 trials are active or planned to determine the safety, efficacy, and feasibility of CAR-T therapy in patients with H3 K27M-mutant disease.

It was previously established that patient-derived H3 K27M-mutant glioma cell cultures over-express the disialoganglioside GD2, and subsequent *in vitro* studies demonstrated the anti-cancer efficacy of anti-GD2 CAR-T cells in murine xenograft models.[56] Currently, early phase trials are assessing the feasibility of anti-GD2 CAR-T cell therapy in patients with H3 K27M-mutant disease. A phase 1 trial assessing the feasibility, safety, and efficacy of GD2-CAR T cell therapy in patients with H3 K27M-mutant DIPG/spinal DMG is currently recruiting (**Table 1**; NCT04196413). Patients with tumor involvement in the cerebellar vermis or hemisphere, thalamus, or supratentorial area are not eligible. The study will evaluate three dose levels and compare intravenous and intracerebroventricular delivery, with primary endpoints of successful manufacture of GD2-CAR-T cells, maximum tolerated dose, and safety. An assessment of the first four patients treated on study found that three patients experienced radiographic and clinical improvement, including improved motor function. Additionally, the presence of TIL in the tumor suggests a conversion to an immunologically hot state. However, safety remains a concern, as immune responses invariably are associated with inflammation, which could present an issue in the brainstem region. As a precaution,

all patients enrolled on trial were therefore required to undergo placement of a ventricular reservoir, allowing rapid monitoring of intracranial pressure and removal of cerebrospinal fluid to mitigate swelling. All four patients experienced cytokine release syndrome. Toxicity was reversible but required intensive supportive inpatient care.[57]

Additionally, the phase 1 CARMIGO trial will assess the feasibility, safety, and efficacy of GD2-CAR T cell therapy in a single-center trial (**Table 1**; NCT05544526). This study, which has not yet begun recruiting, will enroll pediatric and young adult patients with H3 K27M-mutant DMG, and will require placement of an ventricular reservoir prior to treatment. Initial therapy will be delivered intravenously; patients who do not demonstrate a response 28 days following administration and who have not experienced intolerable toxicity will be eligible to receive a second intraventricular administration of CAR-T cells.

CAR-T therapy is also under investigation using a H3 K27M-specific TCR in place of the GD2-specific trials described above. A phase 1 dose-escalation trial will evaluate the dosage and safety of administration of autologous anti-H3.3K27M TCR-expressing CAR-T cells (KIND cells) in HLA-A*02:01-positive pediatric and young adult patients with H3.3K27M-mutated DMG. Treatment will be delivered intravenously. This trial is not yet recruiting. However, similar to the concerns raised around the ultimate viability of the H3 K27M synthetic peptide vaccine, there is some concern that the lack of endogenous processing of the H3 K27M peptide limits the efficacy of therapies relying on immune responses to this antigen.

Lastly, an innovative trial, SC-CAR4BRAIN, is underway to evaluate a quadrivalent CAR-T cell therapy against B7-H3, EGFR806, HER2 and IL13-zetakine. Given the design against four distinct antigens, this trial is of great interest to the neuro-oncology community. This study also requires an indwelling ventricular access device, and is open to patients with pontine and non-pontine DMG (NCT05768880).

Non-CAR-T Cell Adoptive Transfer Therapies

Adoptive transfer is a technology by which transfer of a patient's own immune cells back into their blood stream is performed following ex vivo manipulation. Patients are usually induced to be lymphopenic (lymphodepletion) prior to reintroduction via administration of myeloablative (MA) and non-myeloablative (NMA) chemotherapy, as this has been shown to result in dramatic T cell expansion and potent immunologic responses. There are currently two trials utilizing this approach for treatment of DMG. The first is the BRAVO trial, designed to investigate the efficacy of TMZ, which produces profound lymphopenia in children with CNS tumors, as an adjuvant therapy during and following radiotherapy for newly diagnosed brainstem gliomas (**Table 1,** NCT03396575).[58] In this study, patients receive tumor-specific lymphocytes, expanded ex vivo with the use of TTRNA-pulsed dendritic cells (DCs), that preferentially expand in this lymphopenic environment following TMZ administration, and serve as a source of responder cells to subsequent DC vaccination. The second study utilizing this approach is the PEACH trial (**Table 1,** NCT04837547).[59] This is a phase 1 open-label, multicenter study, to evaluate the safety, feasibility, and MTD of DIPG treatment with adoptive cell therapy (Total tumor mRNA-pulsed autologous DCs (TTRNA-DCs), Tumor-specific ex vivo expanded autologous lymphocyte transfer (TTRNA-xALT) and Autologous G-CSF mobilized Hematopoietic Stem Cells (HSCs)).

Monoclonal Antibodies

One increasingly popular cancer immunotherapy approach is to use monoclonal antibodies to target ligands on immune cells in order to stimulate an immune response to attack cancer cells.[60] Two trials were identified that test this approach for pediatric brain tumor treatment, including HGG and DIPG.

Anti-CD40

First, APX005M is a CD40 agonistic monoclonal antibody that binds to CD40, triggering B cell, monocyte, and dendritic cell activation, and stimulating cytokine release from lymphocytes and monocytes. CD40 is also expressed on many human tumor cells, hence APX005M can mediate a direct cytotoxic effect on CD40+ tumor cells. A multi-center, non-randomized open label Phase I trial (**Table 1,** NCT03389802) is currently underway to evaluate the safety and tolerability of APX005M in children with recurrent or refractory primary malignant central nervous system tumors including HGG or newly diagnosed DIPG.[61]

Anti-PD-1

Pembrolizumab (MK-3475) is an anti-PD-1 monoclonal antibody that acts as an immune checkpoint inhibitor by binding its ligands, PD-L1 and PD-L2. This drug has been investigated as a potential treatment for a variety of high grade pediatric brain tumors, initially including DIPG , through a multi-center, phase 1 open label study supported by the Pediatric Brain Tumor Consortium (**Table 1,** NCT02359565).[62] Unfortunately, the DIPG arm closed early due to worse OS and rapid decline of the patients.[63] In this study, patients aged 1 – 30 years with a recurrent, progressive or refractory DIPG, following radiation therapy with or without chemotherapy, were treated with Pembrolizumab. Primary outcome measures included incidence of AEs within 30 days of treatment, sustained objective response (partial response + complete response) within 12 cycles (approximately 9 months), and the change in the percentage of CD8+ T cells that are PD-1+ due to treatment with pembrolizumab via serial serum testing.

<u>Small Molecules</u>

Despite the prevalence of small molecules for a variety of cancers, few compounds are being evaluated in DIPG and H3 K27M-mutant exclusive populations. Our search identified sixteen clinical trials evaluating small molecules in patients with H3 K27M-mutant disease or DIPG. These studies

are designed to investigate a wide variety of treatment strategies, from immunotherapy to epigenetic targeted agents, as described below.

Selinexor

Selinexor is an inhibitor of exportin-1 (XPO-1), a nuclear export protein that is over expressed in multiple solid tumors, including gliomas, where its upregulation is associated with a worse prognosis.[64] Selinexor was previously approved by the FDA for relapsed/refractory multiple myeloma and relapsed/refractory diffuse large B-cell lymphoma.[65]

In preclinical models of glioblastoma, selinexor demonstrated anti-cancer efficacy in cell lines and murine models.[66] A subsequent phase 2, open-label study of molecularly unselected adults with recurrent glioblastoma evaluated the safety, efficacy, and pharmacokinetics of selinexor monotherapy. Biopsy of patients undergoing resection indicated that intratumor concentrations of selinexor reached therapeutic levels. In a trial on recurrent glioblastoma, the 6-month PFS varied in the various study arms between 7.7 and 17%; further trials are ongoing.[67] As preclinical research has indicated, selinexor may act as a radiosensitizer in models of GBM.[68] A phase 1/2 study of selinexor in combination with radiotherapy is currently being conducted through the Children's Oncology Group in children and young adults with DIPG or H3 K27M-mutant DMG (**Table 1**; NCT05099003). Patients will receive standard of care radiation in combination with selinexor, followed by maintenance selinexor after completion of radiotherapy. The primary objectives include maximum tolerated dose, event free survival, OS, and overall response rate. From study design and protocol information publicly available, it appears that a group of patients in Step 1 will be required to have H3 K27M-mutant disease; however broader populations of patients with H3 K27-WT HGG or DIPG will also be evaluated.

CDK 4/6 Inhibitors

The next category of small molecule inhibitors includes two studies examining the effects of cyclin D-cyclin-dependent kinase (CDK4/6) pathway inhibition. The CDK4/6-p16-retinoblastoma (Rb) pathway is commonly disrupted in cancers, including HGG, resulting in abnormal cell proliferation causing tumorigenesis.[69] Chemotherapeutic agents targeting this CDK4/6 pathway were shown to have antitumor effects in multiple clinical studies of a variety of tumors, and are currently used in combination with hormone therapy to treat some breast cancers. One such CDK4/6 inhibitor, abemaciclib, is being investigated in a non-randomized parallel assignment, phase 1 clinical trial in children and young adults with newly diagnosed DIPG (**Table 1,** NCT02644460).[70] In this study, DIPG patients between 2 -25 years of age will receive RT in 30-33 fractions over approximately 6 weeks. Treatment with oral abemaciclib is initiated with RT, and continues twice daily during and after RT, for a maximum treatment duration of 2 years. Primary outcome measures include determination of the MTD of abemaciclib in DIPG patients, as well as PK properties.

Efficacy of a second CDK4/6 inhibitor, ribocyilib, is being evaluated alone and in combination with everolimus, an mTOR inhibitor (see below) for the treatment of high-grade glioma (HGG) and DIPG (NCT05843253).[71] The rationale for this approach is that CDK4/6 inhibitors alone have not shown response in HGG.[69] In this multi-center, international, phase 2 study, patients aged 12 months to 30 years old with newly diagnosed with HGG or DIPG that harbors alterations of the cell cycle and/or PI3K/mTOR pathways will receive a combination of oral ribociclib and everolimus after receiving radiotherapy (RT). Efficacy (primary outcome measure) is defined by progression-free survival (PFS) in HGG patients (Stratum A), and OS in DIPG patients (Stratum B).

mTOR Inhibition

Dysregulation of mTOR signaling, including PI3K amplification/mutation and PTEN loss of function, has been noted in a variety of cancers. As a result, mTOR inhibitors have been explored alone and in combination as anticancer therapy, including HGG. In addition to the above study examining ribociclib (CDK4/6 inhibitor) with everolimus (mTOR inhibitor), a second mTOR inhibitor, temsirolimus, is currently under clinical trial investigation (**Table1,** NCT02420613) in combination with vorinostat, an HDAC inhibitor (see below).[72] Patients 7 months to 20 years old with newly diagnosed or progressive DIPG may enroll In this single center phase 1, non-randomized, dose-escalation study. The primary goals of the study are to examine the MTD and potential side effects (AEs) of increasing dosage of temsirolimus in combination with vorinostat for DIPG treatment.

FACT complex-targeting Curaxin CBL0137

Curaxin CBL0137 is a molecule that regulates p53 and NF-κB to exert antitumor activity in multiple cancers, including HGG. It is thought that CBL0137 works by binding to tumor DNA through the facilitates chromatin transcription (FACT) complex, targeting cancer stem cell proliferation.[73] Currently one trial is designed to investigate the efficacy of CBL0137 for treatment of CNS tumors, including H3K27M mutant DMG and DIPG **(Table 1,** NCT04870944). The goal of this phase 2 study is to determine the MTD of CBL0137, and to determine the ORR in children with progressive/recurrent DIPG and other H3 K27M-mutant DMG.

HDAC Inhibition

Because of the distinct epigenetic events driving DMG and H3K27M mutant glioma formation, studies to investigate multiple different epigenetic targeted therapies have been performed or are currently underway. One such strategy includes inhibition of a family of enzymes known as histone deacetylases (HDAC), which effectively maintains an acetylated histone state to promote expression of tumor suppressor genes and inhibit oncogene expression. While a phase I/II

study of vorinostat and radiotherapy in patients with newly diagnosed DIPG failed to demonstrate improved outcome measures relative to historical controls,[74] two clinical trials of HDAC inhibition in DIPG and/or H3K27M mutant glioma were identified by our search.

The first is a multi-center, early phase 1 (target validation) study examining fimepinostat in children and young adults with newly diagnosed DIPG, recurrent medulloblastoma, or recurrent HGG (NCT03893487).[75] In this study, patients 3-39 years old will receive oral fimepinostat, then drug and metabolite concentration will be measured in primary tumor tissue post-treatment to confirm penetration of fimepinostat across the blood brain barrier (BBB, primary objective).

The second trial is a study of the efficacy of panobinostat, a histone deacetylase (HDAC) inhibitor, for the treatment of DIPG (**Table 1,** NCT02717455). Panobinostat also induces expression of cell-cycle control genes including CDKN1A (p21), and selectively inhibits tumor cell proliferation in DIPG cell cultures and orthotopic xenograft models. This phase 1 study of panobinostat in children with recurrent/progressive DIPG has been accruing subjects since 2016, with the goal of determining the MTD and PK properties of the drug.

Proteasome Inhibition

A variety of proteosome inhibitors are currently under clinical trial for different cancer types, including glioma. It is generally understood that proteasome inhibitors prevent degradation of pro-apoptotic molecules, including p53, thereby promoting apoptosis. One such molecule is Marizomib, which is currently under investigation for treatment of newly diagnosed DIPG (NCT04341311) in combination with Panobinostat (see HDAC inhibition above).[76] This single-center, phase 1, non-randomized trial for DIPG patients up to 21 years old consists of two parts. First, the MTD of IV Marizomib will be determined. Next, subjects who tolerate IV Marizomib alone will be treated with IV Marizomib and oral Panobinostat, but at lower dose of Marizomib than the dose of marizomib

when given alone. Primary outcome measures are determination of the MTD and dose limiting toxicity (DLT) for Marizomib alone and Marizomib in combination with Panobinostat, as well as pharmacokinetic properties.

HIF1-alpha and VEGFR2 Expression Targeting

OKN-007 is a small molecule agent that inhibits both HIF-1 protein expression and vascular endothelial growth factor receptor 2 (VEGFR2) protein expression in glioma, thereby impeding tumor angiogenesis.[77] OKN-007 has also been shown to increase glioma cell apoptosis.[77] Given these properties, OKN-007 has been evaluated in murine models of DIPG[78], and is now being evaluated in recurrent glioblastoma; expanded access for DIPG patients is currently underway (**Table 1,** NCT05518838).

Indoleamine 2,3-dioxygenase (IDO) Inhibition

Amongst immunotherapeutic strategies, Indoleamine 2,3-dioxygenase (IDO) inhibition has been investigated for a variety of cancer types, including glioma. IDO is tryptophan-degrading enzyme that has been found to be expressed by cancer cells. Tumor cell expression of IDO has an immunosuppressive effect, increasing apoptosis of cytotoxic T lymphocytes (CTL) and converting naïve T cells into inducible immunosuppressive regulatory T cells (Tregs; CD4 + CD25 + FoxP3 +).[79.] As such, targeting this metabolic pathway can enhance the immune response against tumor cells. One trial of this strategy for brain tumor treatment, including DIPG, is currently recruiting (NCT04049669).[80] This phase 2, non-randomized, open label, multi-center trial is designed to investigate the efficacy of brain tumor treatment with the oral IDO inhibitor Indoximod and radiation therapy (RT) in combination with temozolomide, with etoposide, cyclophosphamide and/or lomustine for salvage therapy. This investigation consists of four distinct cohorts of patients: those with progressive glioblastoma, medulloblastoma or ependymoma, and those with newly-diagnosed

DIPG (no prior radiation or other therapy, biopsy not required). For DIPG patients, the primary outcome measure of this study 12 month OS.

ClpP/DRD2 Targeting

ONC201 is a first-in-class small molecule first-in-class dopamine receptor D2 (DRD2) antagonism and caseinolytic protease P (ClpP) agonist.{Jackson, 2023 #11079} ONC201 has been evaluated in several glioma trials and recently, an integrated analysis of five open-label studies found that the monotherapy ORR assessed by blinded independent central review using RANO-HGG and RANO-LGG criteria among pediatric and adult patients with recurrent H3 K27M DMG was 30.0%, with no treatment-related grade 4 TEAEs, deaths, or discontinuations reported; median duration of response and time to response were 11.2 months (95%CI, 3.8–not reached) and 8.3 months (range, 1.9–15.9), respectively. [Arrillaga-Romany, *Under submission*, 2023] Previous research has confirmed that oral ONC201 administration results in therapeutic intratumoral concentrations,[81] efficacy in non-midline H3 K27M-mutant diffuse gliomas (Odia, 2023), reduction in H3 K27M circulating tumor DNA in cerebrospinal fluid following ONC201 treatment, and reversal of H3 K27 trimethylation loss, which is a hallmark characteristic of the H3 K27M mutation and independently associated with negative prognosis. (Koschmann 2023).

There are currently five active clinical trials evaluating ONC201 in at least one treatment arm or cohort that proactively requires the presence of the H3 K27M mutation; of these, an expanded access protocol and the phase three trial are currently recruiting patients, and the remaining three are closed to further enrollment. The expanded access protocol (**Table 1**; NCT04617002) is available for pediatric and young adult patients with H3 K27M-mutant glioma who previously received radiotherapy and are not eligible for other ongoing ONC201 trials. ONC201 will be taken once-weekly; adult patients will receive 625 mg and pediatric patients will receive a dose scaled by body weight.

A phase 1 trial of ONC201 in pediatric patients with newly diagnosed DIPG and relapsed/refractory pediatric glioma (**Table 1**, NCT03416530) is currently assessing several ONC201 formulations and treatment schedules, including twice-weekly dosing on consecutive days (Gardner, et al, 2023). The primary objective is determination of the recommended phase 2 dose. Requirements for H3 K27M status vary by cohort; some arms of the trial require H3 K27M-mutant glioma.

A phase 2 trial of young adult and adult patients (≥16 years old) is assessing ONC201 in recurrent high-grade glioma (**Table 1**; NCT02525692). This study has several treatment arms, including one which requires H3 K27M mutant disease. The primary objective is 6-month PFS.

A phase 2 trial is assessing ONC201 in adults with recurrent H3 K27M-mutant HGG (**Table 1**; NCT03295396). All treatment arms require H3 K27M-mutant disease. The primary endpoint is best overall response.

Finally, ACTION, a phase 3, randomized, placebo-controlled study of ONC201 following radiotherapy in adult and pediatric patients with newly diagnosed, H3 K27M-mutant diffuse glioma is currently enrolling (**Table 1**; NCT05580562). Eligible patients who are 2-6 weeks from prior radiation are randomized 1:1:1 to received twice-weekly ONC201, once-weekly ONC201, or placebo. Pontine and spinal tumors are excluded from this study. The primary endpoints are overall survival and progression free survival by RANO-HGG criteria per BICR. ACTION is currently enrolling at global sites, and the study design and eligibility criteria are discussed in detail in Arrillaga-Romany, et al (2023).

Of note, a recent report by Cantor et al demonstrates the feasibility of cell-free tumor DNA tracking to predict ONC201 treatment response and disease progression in DMG.[82] This approach has great potential to improve the clinical care and outcomes of these patients via treatment stratification and longitudinal response monitoring, without the need to repeat tissue biopsy.

Delivery Enhancement

Focused Ultrasound

An area of novel research is investigation of the use of focused ultrasound (FUS) to open the blood brain barrier (BBB), to improve delivery, and thereby efficacy, of chemotherapeutics targeted to H3K27M mutant disease and DIPG. FUS is a technique whereby microbubbles and neuro-navigator controlled sonication opens the BBB non-invasively. This technique is currently being applied in clinical trials for the treatment for a variety of brain tumor types, including glioblastoma and DMG, after being demonstrated to be safe and effective in mouse models of disease.[83-86] A total of four distinct clinical trials investigating the use of FUS for H3K27M mutant disease and/or DIPG or DMG treatment were identified on clinicaltrials.gov using the current described search of the literature.

The first study is being conducted by Wu and colleagues at Columbia University in New York, NY in order to examine the efficacy of oral Panobinostat administration with the use of FUS (**table 1,** NCT04804709). The purpose of this study is to evaluate the safety and feasibility of BBB opening with FUS in young patients with progressive/recurrent DMG. In this study, patients aged 4-21 years with clinical and/or radiographic progression of DMG (defined as a radiological diagnosis of with tumor involving the pons, thalami and/or histological confirmation of H3K27M mutation in a pontine or thalamic glioma), are being actively enrolled. All patients will be treated with FUS, followed by administration of 15 mg of oral Panobinostat. The trial then will follow a 3+3 Number of Tumor Sites (NOTS) escalation design, with the NOTS defined as the number of openings created in the BBB using FUS, increased incrementally from one to three if no dose-limiting toxicities (DLTs) are observed. The primary outcome measure is the number of adverse events measured up to 90 days after the end of the last FUS treatment,

A second trial by the same investigators is being conducted to examine the feasibility of FUS enhanced delivery of etoposide chemotherapy for DMG patients (**Table 1,** NCT05762419). Patients aged 4-21 years with DMG are being actively enrolled. Subjects will receive FUS followed by once daily oral etoposide (50mg) taken every day for 21 days, followed by one week of rest. In the first cycle, etoposide will be administered immediately following radiographic (MRI) confirmation of BBB opening, which must be performed within four hours of FUS treatment. For subsequent cycles (maximum four), etoposide will be administered immediately following the FUS procedure. Primary outcome measures include the number of adverse events AEs measured up to 90 days after the end of the last FUS treatment, and the number of patients with successful opening of the BBB as measured by contrast-enhanced MRI.

Another study is being conducted (**Table 1,** NCT05615623)[87] to investigate the safety, feasibility and preliminary efficacy of FUS in pediatric patients with DIPG undergoing Doxorubicin chemotherapy. In this prospective, single arm, non-randomized feasibility study, patients 5-18 years old with DIPG will undergo three treatment cycles, approximately 4 -6 weeks apart. The primary outcome measure for these studies is any adverse event after treatment until the conclusion of the study (2 years).

Lastly, a multicenter study is currently being conducted to investigate the safety and tolerability of sonodynamic therapy (SDT) using SONALA-001 and Exablate Type-2 device, and to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of MR-Guided Focused Ultrasound (MRgFUS) energy in combination with SONALA-001 (ALA) in subjects with DIPG (**Table 1,** NCT05123534).[88] To be eligible for this non-randomized, dose-escalation study, patients aged 5 years or older must have newly diagnosed, radiographically typical DIPG with or without histologic confirmation. MTD of SONALA-001 and Exablate 4000 Type-2 in combination will be determined. SONALA-001 will be given 6-9 hours prior to receiving one of three energy levels of MRgFUS. Primary outcome measures include safety and tolerability of dose escalation, as measured

by the frequency and severity of dose-limiting toxicities (DLTs), AEs, and the MTD of MRgFUS energy in combination with SONALA-001. Additional secondary outcomes include: the mechanical performance of Exablate 4000 Type 2.0 device, and the PK of ALA and Protoporphyrin IX (PpIX) following IV dosing with SONALA-001.

Other Novel Interventions

There remain three additional trials for H3K27M glioma and DIPG treatment that warrant mention here. These studies all employ novel approaches to anti-cancer therapy. The first is an investigation of the safety and efficacy of BXQ-350 for treatment of newly diagnosed DIPG or DMG (**Table 1,** NCT04771897). BXQ-350 is a novel agent configured from two components: Saposin C (SapC), an expressed (human) lysosomal protein, and the phospholipid 26 oleoyllphosphatidyl-serine (DOPS), a cell membrane phospholipid. This Phase I study will focus on establishing the MTD of BXQ-350, then measuring drug concentrations in biopsied DMG tissue, including DIPG.

The second study of interest is an investigation of the utility of an oncolytic virus, AloCELYVIR, in treating newly diagnosed DIPG in combination with radiotherapy (**Table 1,** NCT04758533).[89] In this open, non-randomized, single-center Phase I clinical trial, patients aged 1-21 years with previously untreated DIPG are treated with AloCELYVIR infusion (bone marrow derived allogenic mesenchymal allogenic cells infected with the an oncolytic adenovirus) ICOVIR-5, a potent and selective oncolytic adenovirus based on the pRB pathway) weekly over the course of eight weeks, with dose limiting toxicity (DLT) determination at one month as a primary outcome measure.

The last is the application of tumor-treating fields using the Optune device in combination with radiation therapy for the treatment of DIPG (NCT03033992). The Optune System produces alternating electrical fields, called tumor treatment fields (TTFields) via 4 transducer arrays placed on the shaved scalp. The very low intensity, intermediate frequency electric fields impair the growth of

tumor cells by arresting cell division and inducing apoptosis. Preclinical studies have demonstrated TTFields synergistically enhance the efficacy of irradiation in glioma cell lines, therefore in this trial children with DIPG will also receive concurrent standard RT. This single arm trial will focus on the feasibility of wearing the Optune device ≥18 hours per day, and the safety and efficacy of Optune treatment with standard RT for DIPG patients.

Conclusions

Despite the recognition of H3 K27M as a molecular alteration defining a class of HGG[3,90], to date this has failed to improve the established treatment paradigm. Several clinical trials are currently ongoing that focus specifically on this disease subset, as well as for treatment of diffuse midline gliomas of the brainstem that may or may not carry this mutation (DIPG). At writing, 642 planned, recruiting, or active interventional brain cancer trials were indexed on clinicaltrials.gov. In contrast, a search for H3 K27M-mutant disease and/or DIPG identified only 41 such trials that proactively included treatment arms or cohorts to evaluate therapeutics in an exclusive population of patients with these conditions. The main three categories of therapeutics currently under clinical evaluation for this patient population are chemotherapy, vaccines, adoptive transfer therapy, small molecules, and focused ultrasound.

Our summary of clinical trials conducted in H3 K27M-mutant disease and DIPG has limitations. The intention of the search strategy was to identify trials focusing on H3 K27M-mutant glioma and DIPG. However, due to the variation in detail provided on clinicaltrials.gov, the structure of some analyses and groups is not universally detailed. In our selection of trials for inclusion here, many studies were excluded, as they did not detail in their listing a treatment arm or cohort evaluating the intervention exclusively in a population of patients with H3 K27M or diffuse midline glioma, including DIPG. However, it is possible that some trials intend to evaluate interventions in this disease subset, but did not provide sufficient detail in the clincialtrials.gov listing for qualification for this summary. Of note, additional resources exist, including the DIPG Registry and DIPG Trials

Toolbox, which are designed to help pair families with existing clinical trials for DIPG. Some notable analyses and treatments that may have relevance for treatment of H3 K27M-mutant diffuse glioma were therefore omitted, including a retrospective analysis of panobinostat in adults with H3 K27M-mutant DMG, which demonstrated tolerability and a median overall survival of 42 months,[91] and the Biological Medicine for Diffuse DIPG Eradication (BIOMEDE trials). The first BIOMEDE trial evaluated erlotinib, dasitinib, and everolimus in pediatric patients with diffuse pontine glioma, and BIOMEDE 2.0 (**Supplemental Table 1**, NCT05476939) evaluates everolimus, ONC201, and radiotherapy in patients with DIPG or H3 K27M-mutant DMG. Additionally, a phase 2 trial evaluating ONC201 in combination with panobinostat or paxalisib is currently underway in pediatric and young adult patients with DMG; while H3 K27M is not required for eligibility, it is permitted in several cohorts (NCT05009992).

A final major development in the care and management of DMGs that warrants mention is the advent of stereotactic tumor biopsy for histological diagnosis and molecular analysis of these deep seated, unresectable tumors. To this end, an important multi-center study utilizing upfront biology-guided treatment, including tumor biopsy tissue as well as liquid biopsy specimens, was recently completed.[92] In this study, DIPG patients underwent tumor biopsy, and tissue was submitted for whole-exome and mRNA sequencing. After undergoing standard radiotherapy treatment, molecular data was reviewed by a tumor board and patients were subsequently assigned up to four FDA-approved drugs. H3K27M-mutant circulating tumor DNA (ctDNA) was also longitudinally measured throughout diagnosis and treatment in blood serum, predicting response to therapy and disease recurrence. While not included in our systematic analysis (due to having been completed), this groundbreaking study demonstrates the feasibility of molecular subtyping for treatment stratification and lays the foundation for future liquid biopsy for clinical correlates of treatment response and resistance.

Despite strides in understanding of the molecular underpinnings of DMG and H3 K27M-mutant disease, few therapies have demonstrated efficacy in this population. There is a significant unmet need for treatments effective in patients with H3 K27M-mutant disease. Due to the relatively rare patient population, enrollment of patients in active clinical trials will be vital in the development and eventual approval of novel therapies in this indication.

Acknowledgements

Medical writing and editorial support were provided by Meghan Sullivan, PhD, CMPP, an employee of Chimerix, Inc. This article appears as part of the supplement "H3 K27M-mutant Glioma: Disease State Overview," sponsored by Chimerix, Inc.

COI

MvdB, MG, and EF have no relevant conflicts of interest to declare. AMS is a paid consultant of Chimerix, Inc.

Author Contributions

- Study Design: MvdB, MG, EF, ASM
- Data Collection: non-applicable
- Statistical Analyses: non-applicable
- Manuscript Preparation: MvdB, MG, EF, ASM
- Manuscript Review: MvdB, MG, EF, ASM

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Table 1. Summary of Studies on ClinicalTrials.gov for Patients with H3 K27M-mutant or H3K27-altered Disease and/or DIPG

NCT Number	Phase	Study Title	Study Status	Therapy Type	Age
Chemotherapy					
NCT03257631	Ph 2	A Study of Pomalidomide Monotherapy for Children and Young Adults With Recurrent or Progressive Primary Brain Tumors	Active, Not Recruiting	Chemotherapy	Child, Adult
NCT02992015	Ph 1	Gemcitabine in Newly-Diagnosed Diffuse Intrinsic Pontine Glioma	Recruiting	Chemotherapy	Child
Re-irradiation					
NCT03126266	Ph 2	Re-Irradiation of Progressive or Recurrent DIPG	Recruiting	Radiation	Child, Adult, Older Adult
Vaccination					
NCT02960230	Ph 1/2	H3.3K27M Peptide Vaccine With Nivolumab for Children With Newly Diagnosed DIPG and Other Gliomas	Active, Not Recruiting	Vaccine: K27M	Child, Adult
NCT04749641	Ph 1	Neoantigen Vaccine Therapy Against H3.3-K27M Diffuse Intrinsic Pontine Glioma	Recruiting	Vaccine: K27M	Child, Adult, Older Adult
NCT04808245	Ph 1	A MultIceNTER Phase I Peptide VaCcine Trial for the Treatment of H3-Mutated Gliomas	Recruiting	Vaccine: K27M	Adult, Older Adult
NCT05096481	Ph 2	PEP-CMV Vaccine Targeting CMV Antigen to Treat Newly Diagnosed Pediatric HGG and DIPG and Recurrent Medulloblastoma	Not Yet Recruiting	Vaccine: CMV (pp65)	Child, Adult
NCT04943848	Ph 1	rHSC-DIPGVax Plus Checkpoint Blockade for the Treatment of Newly Diagnosed DIPG and DMG	Recruiting	Vaccine: Neo-epitopes	Child, Adult
Adoptive Transfer					
NCT05478837	Ph 1	Genetically Modified Cells (KIND T Cells) for the Treatment of HLA-A*0201-Positive Patients With H3.3K27M-Mutated Glioma	Not Yet Recruiting	Adoptive Transfer: CAR-T	Child, Adult

NCT05544526	Ph 1	CAR T Cells to Target GD2 for DMG	Not Yet Recruiting	Adoptive Transfer: CAR-T	Child
NCT04185038	Ph 1	Study of B7-H3-Specific CAR T Cell Locoregional Immunotherapy for Diffuse Intrinsic Pontine Glioma/Diffuse Midline Glioma and Recurrent or Refractory Pediatric Central Nervous System Tumors	Recruiting	Adoptive Transfer: CAR-T	Child, Adult
NCT05768880	Ph 1	Study of B7-H3, EGFR806, HER2, And IL13-Zetakine (Quad) CAR T Cell Locoregional Immunotherapy For Pediatric Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, And Recurrent Or Refractory Central Nervous System Tumors	Recruiting	Adoptive Transfer: CAR-T	Child, Adult
NCT04196413	Ph 1	GD2 CAR T Cells in Diffuse Intrinsic Pontine Gliomas(DIPG) & Spinal Diffuse Midline Glioma(DMG)	Recruiting	Adoptive Transfer: CAR-T	Child, Adult
NCT03396575	Ph 1	Brain Stem Gliomas Treated With Adoptive Cellular Therapy During Focal Radiotherapy Recovery Alone or With Dose-intensified Temozolomide (Phase I)	Recruiting	Adoptive Transfer: Non-CAR-T	Child, Adult
NCT04837547	Ph 1	PEACH TRIAL- Precision Medicine and Adoptive Cellular Therapy	Recruiting	Adoptive transfer: Non-CAR-T | Vaccine: Tumor Ag-pulsed DCs	Child, Adult
Monoclonal Antibodies					
NCT03389802	Ph 1	Phase I Study of APX005M in Pediatric CNS Tumors	Active, Not Recruiting	Monoclonal Antibodies: anti-CD40	Child, Adult
NCT02359565	Ph 1	Pembrolizumab in Treating Younger Patients With Recurrent, Progressive, or Refractory High-Grade Gliomas, Diffuse Intrinsic Pontine Gliomas, Hypermutated Brain Tumors, Ependymoma or Medulloblastoma	Recruiting	Monoclonal Antibodies: anti-PD1	Child, Adult
Small Molecules					
NCT05099003	Ph 1/2	A Study of the Drug Selinexor With Radiation Therapy in Patients With Newly-Diagnosed	Recruiting	Small molecule: selective inhibitor of nuclear export	Child, Adult

		Diffuse Intrinsic Pontine (DIPG) Glioma and High-Grade Glioma (HGG)		(SINE)	
NCT02644460	Ph 1	Abemaciclib in Children With DIPG or Recurrent/Refractory Solid Tumors	Recruiting	Small Molecule: CDK4/6 inhibitor	Child, Adult
NCT05843253	Ph 2	Study of Ribociclib and Everolimus in HGG and DIPG	Not Yet Recruiting	Small Molecule: CDK4/6 inhibitor | Small molecule: mTOR inhibitor	Child, Adult
NCT02420613	Ph 1	Vorinostat and Temsirolimus With or Without Radiation Therapy in Treating Younger Patients With Newly Diagnosed or Progressive Diffuse Intrinsic Pontine Glioma	Active, Not Recruiting	Small Molecule: mTOR inhibitor	Child, Adult
NCT04870944	Ph 1/2	CBL0137 for the Treatment of Relapsed or Refractory Solid Tumors, Including CNS Tumors and Lymphoma	Active, Not Recruiting	Small molecule: FACT Sequesteration	Child, Adult
NCT03893487	Ph 1	Fimepinostat in Treating Brain Tumors in Children and Young Adults	Active, Not Recruiting	Small molecule: HDAC and PI3K Inhibitor	Child, Adult
NCT02717455	Ph 1	Trial of Panobinostat in Children With Diffuse Intrinsic Pontine Glioma	Active, Not Recruiting	Small molecule: HDAC Inhibitor	Child, Adult
NCT04341311	Ph 1	Phase I Study of Marizomib + Panobinostat for Children With DIPG	Active, Not Recruiting	Small molecule: Proteasome inhibitor	Child, Adult
NCT05518838	EAP	Expanded Access to OKN-007 for Patients With Diffuse Midline Glioma, H3 K27-altered	Available	Small Molecule: HIF1-alpha and VEGFR2 expression	Child, Adult
NCT04049669	Ph 2	Pediatric Trial of Indoximod With Chemotherapy and Radiation for Relapsed Brain Tumors or Newly Diagnosed DIPG	Recruiting	Small molecule: indoleamine 2,3-dioxygenase (IDO) inhibitor	Child, Adult
NCT02525692	Ph 2	Oral ONC201 in Recurrent GBM, H3 K27M Glioma, and Midline Glioma	Active, Not Recruiting	Small Molecule: Imipridone	Child, Adult, Older Adult
NCT03295396	Ph 2	ONC201 in Adults With Recurrent H3 K27M-mutant Glioma	Active, Not Recruiting	Small Molecule: Imipridone	Adult, Older Adult
NCT03416530	Ph 1	ONC201 in Pediatric H3 K27M Gliomas	Active, Not Recruiting	Small Molecule: Imipridone	Child, Adult
NCT04617002	EAP	Intermediate-size Expanded Access to ONC201 for Patients With H3 K27M-mutant and/or Midline Gliomas	Available	Small Molecule: Imipridone	Child, Adult, Older Adult

NCT05476939	Ph 3	Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication 2.0	Recruiting	Small Molecule: Imipridone	Child, Adult, Older Adult
NCT05580562	Ph 3	ONC201 in H3 K27M-mutant Diffuse Glioma Following Radiotherapy (the ACTION Study)	Recruiting	Small Molecule: Imipridone	Child, Adult, Older Adult
Enhanced Delivery					
NCT04804709	Ph 1	Non-Invasive Focused Ultrasound (FUS) With Oral Panobinostat in Children With Progressive Diffuse Midline Glioma (DMG)	Active, Not Recruiting	FUS	Child, Adult
NCT05123534	Ph 1/2	A Phase 1/2 Study of Sonodynamic Therapy Using SONALA-001 and Exablate 4000 Type 2 in Patients With DIPG	Recruiting	FUS	Child, Adult, Older Adult
NCT05615623	Ph 1/2	Blood Brain Barrier (BBB) Disruption Using Exablate Focused Ultrasound With Doxorubicin for Treatment of Pediatric DIPG	Recruiting	FUS	Child, Adult
NCT05630209	Ph 1/2	Blood Brain Barrier (BBB) Disruption Using Exablate Focused Ultrasound With Doxorubicin for Treatment of Pediatric DIPG	Recruiting	FUS	Child, Adult
NCT05762419	Ph 1	FUS Etoposide for DMG - A Feasibility Study	Recruiting	FUS	Child, Adult
Other Therapies					
NCT04771897	Ph 1	A Study of BXQ-350 in Children With Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG) or Diffuse Midline Glioma (DMG)	Recruiting	Novel/Unclassed: SapC-Nanovesicle	Child, Adult
NCT04758533	Ph 1/2	Clinical Trial to Assess the Safety and Efficacy of AloCELYVIR With Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG) in Combination With Radiotherapy or Medulloblastoma in Monotherapy	Recruiting	Oncolytic Virus	Child, Adult
NCT03033992	Ph 1/2	Optune for Children With High-Grade Glioma or Ependymoma, and Optune With Radiation Therapy for Children With DIPG	Active, Not Recruiting	Tumor-treating field	Child, Adult

NOW ENROLLING

Phase 2b study of IGV-001 in patients with newly diagnosed glioblastoma (NCT04485949)

OBJECTIVES

PRIMARY OBJECTIVE
Progression-free survival

SECONDARY OBJECTIVE
Overall survival

SAFETY OBJECTIVE
Safety and tolerability

CRITERIA

Key Inclusion Criteria

Patients who take part in the trial* must:

- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

Key Exclusion Criteria

Patients are not allowed to participate* in the trial if they have:

- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn's disease)
- Heart disease or history of heart issues

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clinicaltrials.gov/ct2/show/NCT04485949

*Additional criteria apply. Please refer to protocol 14379-201 for full inclusion and exclusion criteria. †Patients can participate if they had some skin cancers, superficial bladder cancer (cancer that was only on the surface of the lining of the bladder), or carcinoma in situ (cancer that had not spread) of the cervix or breast that had been cured.

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IGF-1R, insulin-like growth factor 1 receptor; KPS, Karnofsky Performance Scale; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.