ACTION: A randomized phase 3 study of ONC201 (dordaviprone) in patients with newly diagnosed H3 K27M-mutant diffuse glioma

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Abstract

Background: H3 K27M-mutant diffuse glioma primarily affects children and young adults, is associated with a poor prognosis, and no effective systemic therapy is currently available. ONC201 (dordaviprone) has previously demonstrated efficacy in patients with recurrent disease. This phase 3 trial evaluates ONC201 in patients with newly diagnosed H3 K27M-mutant glioma.

Methods: ACTION (NCT05580562) is a randomized, double-blind, placebo-controlled, parallel-group, international Phase 3 study of ONC201 in newly diagnosed H3 K27M-mutant diffuse glioma. Patients who have completed standard frontline radiotherapy are randomized 1:1:1 to receive placebo, once-weekly dordaviprone, or twice-weekly dordaviprone on two consecutive days. Primary efficacy endpoints are overall survival (OS) and progression-free survival (PFS); PFS is assessed by response assessment in neuro-oncology-high grade glioma criteria (RANO-HGG) by blind independent central review. Secondary objectives include safety, additional efficacy endpoints, clinical benefit, and quality of life. Eligible patients have histologically confirmed H3 K27M-mutant diffuse glioma, a Karnofsky/Lansky performance status ≥70, and completed first-line radiotherapy. Eligibility is not restricted by age; however, patients must be ≥10 kg at time of randomization. Patients with a primary spinal tumor, diffuse intrinsic pontine glioma, leptomeningeal disease, or cerebrospinal fluid dissemination are not eligible. ACTION is currently enrolling in multiple international sites.

Keyword: ONC201, dordaviprone, Phase 3, diffuse glioma, H3 K27M

Key points:

- H3 K27M-mutant diffuse glioma has a poor prognosis and no effective, systemic treatment options.
- ACTION is an international phase 3 trial evaluating the imipridone ONC201 in patients with H3 K27M-mutant diffuse glioma.

Importance of Study:

With no effective treatments other than radiation and a median overall survival of approximately one year, H3 K27M-mutant diffuse glioma requires novel, effective therapies. ONC201 (dordaviprone), is an oral antagonist of dopamine receptor D2 and agonist of ClpP that has previously demonstrated safety and efficacy in open-label trials of patients with recurrent H3 K27M-mutant diffuse glioma. ACTION (NCT05580562) is an international, randomized, double-blind, placebo-controlled, phase 3 trial of ONC201 in adult and pediatric patients with H3 K27M-mutant diffuse glioma, and was designed to serve as the basis for potential regulatory approval.

Introduction

The H3 K27M mutation is a histone mutation observed in up to 70% of pediatric cases of diffuse intrinsic pontine glioma (DIPG) and 60% of adult patients with diffuse midline glioma (DMG), where it is associated with a poor prognosis and aggressive disease course.[1-3] Overall survival (OS) for patients with H3 K27M-mutant glioma is approximately one year, with a one-year OS rate of 55.9%.[3,4] In 2016, the World Health Organization classified H3 K27M-mutant DMG as a distinct form of Grade IV glioma, regardless of histological features, which is characterized by poor prognosis and global loss of H3 K27 trimethylation (H3 K27me3-loss).[5] In the 2021 update of this criteria, the definition was further refined and extended to "diffuse midline glioma, H3 K27-altered" to be inclusive of DMGs that exhibit H3 K27me3-loss due to the H3 K27M mutation or other molecular culprits such as EZHIP[6] Despite the appreciation of H3 K27M status as an important diagnostic factor with a dismal prognosis[7,8], the standard of care for these patients remains radiation followed by monitoring; no effective, systemic therapies are currently available.

ONC201 (dordaviprone) has demonstrated anti-tumor efficacy in preclinical and clinical evaluations of H3 K27M-mutant glioma.[9,10] ONC201 is a first-in-class small molecule, bitopic antagonist of dopamine receptor D2/3 (DRD2/3) and allosteric agonist of the mitochondrial protease caseinolytic mitochondrial matrix peptidase proteolytic subunit (ClpP).[11-15] In the clinic, early clinical trials established therapeutic intratumoral concentrations were achieved in recurrent glioblastoma patients following oral administration of ONC201, without any reports of dose-limiting toxicities. In a phase 2 study of molecularly unselected patients with

glioblastoma, the only patient to achieve a durable, radiographic response to monotherapy ONC201 incidentally harbored the H3 K27M-mutation.

Subsequently, an integrated efficacy and safety analysis of 50 patients from five open-label clinical studies was designed with input from regulatory authorities to evaluate the safety and efficacy of ONC201 in patients with recurrent H3 K27M-mutant DMG, with a primary endpoint of overall response rate (ORR) by response assessment in neuro-oncology (RANO) high-grade glioma (HGG) criteria.[16] The eligibility criteria for the integrated analysis were designed to isolate the single-agent activity of ONC201 in this patient population (eg, patients were treated at least 90 days from prior radiotherapy). The ORR by RANO-HGG criteria was 20.0% (95%CI, 10.0-33.7); ORR using best response by either HGG or low-grade glioma (LGG) RANO criteria was 30.0% (95%CI, 17.9–44.6). Duration of response by RANO-HGG was 11.2 months (95%CI, 3.8–not reached) and median time to response was 8.3 months (range, 1.9–15.9). Additionally, 46.7% of patients on corticosteroids at baseline had >50% decreases in steroid dose and 20.6% of patients with performance status deficiencies at baseline demonstrated an increase in performance status score. A subgroup analysis suggested that responders tended to have a higher baseline performance score and a single target lesion. Both of these characteristics may be enriched in the frontline setting relative to the recurrent setting[17] Recently, an analysis of H3 K27M DMG patients treated with ONC201 following frontline radiation reported a 21.7 months median OS from diagnosis compared to 12 months for historical control patients.[18]

Based on these findings, the phase 3 ACTION trial (NCT05580562) was developed to assess the safety and efficacy of once- or twice-weekly ONC201 in a double-blind, placebo-controlled

randomized clinical trial in pediatric and adult patients with newly diagnosed H3 K27M-mutant diffuse glioma.

Study Design

ACTION (ONC201-108, NCT05580562) is a phase 3, randomized, double-blind, placebo-controlled international trial that is evaluating ONC201 following standard of care radiotherapy in pediatric and adult patients with newly diagnosed, H3 K27M-mutant diffuse glioma. The protocol, any amendments, informed consent forms, investigators brochure, and other relevant materials must be reviewed and approved by each site's institutional review board.

Study eligibility requires known evidence of the H3 K27M-mutation by immunohistochemistry or gene sequencing of the tumor in a CLIA or equivalent setting. Patients must be randomized two to six weeks following completion of radiotherapy and must be randomized within 21 days of their post-radiotherapy MRI. Patients are randomized 1:1:1 to receive twice-weekly ONC201, once-weekly ONC201, or placebo (**Figure 1**). Stratification factors include age (<21 years; ≥21 years) and a risk category based on the presence of enhancing tumors ≥10 cm^2, multifocal lesions, and/or brainstem tumor location. All patients receive ONC201 or placebo capsules on two consecutive days (day 1 and day 2) each week. In the twice-weekly treatment arm, ONC201 is be administered on both day 1 and day 2. In the once-weekly treatment cohort, ONC201 is be administered on day 1, followed by a placebo dose on day 2. The placebo arm receives placebo on both days. Treatment and study assessments is based on 28-day cycles.

ONC201 is administered at 625 mg per dose to patients weighing at least 52.5 kg; patients weighing less than 52.5 kg receive a dose scaled by body weight and rounded to the nearest 125 mg capsule or matching placebo (**Supplemental Table 1**). For patients unable to swallow capsules, ONC201 can be extemporaneously dissolved in approved diluents.

Treatment continues at least until confirmed disease progression, unacceptable adverse event, withdrawal of consent, or change in the patient's condition judged by the treating physician to render the patient ineligible for further treatment (complete reasons for discontinuation are shown in **Supplemental Table 2**). Among patients with confirmed progression, treatment beyond first progression is permitted at the investigator's discretion and may be administered with concomitant bevacizumab or reirradiation. Gadolinium-enhanced MRI is performed approximately every eight weeks. Treatment with ONC201 beyond first progression discontinues if patients initiate an anti-cancer therapy other than bevacizumab and/or re-irradiation. Patients who discontinue treatment can continue to be followed for safety assessment until death, withdrawal of consent to follow-up, or study completion. Dose modifications such as treatment discontinuation, treatment interruption, and dose reduction may be implemented in the event of grade 3/4 treatment-related, treatment-emergent adverse events or grade 4 any-cause adverse events of special interest (**Supplemental Table 3).**

Objectives

The primary objective of the study is to evaluate the efficacy of ONC201; primary endpoints are OS and progression-free survival (PFS) by RANO-HGG criteria. Secondary objectives include safety, additionally efficacy assessments, clinical benefit, and quality of life. A summary of primary and secondary objectives and endpoints in available in **Table 1.**

Patients

Eligible patients must weigh at least 10 kg, have been diagnosed with H3 K27M-mutant diffuse glioma, and have completed standard radiotherapy (54 to 60 Gy at 1.8 to 2.2 Gy/fraction) within two to six weeks of randomization. H3 K27M mutational status must be identified using immunohistochemistry or gene sequencing of the tumor in a clinical laboratory improvement amendments (CLIA)-approved laboratory or equivalent setting. Eligible patients must have a KPS/LPS of at least 70, be receiving a stable or decreasing dose of corticosteroids and anti-seizure medications for seven days prior to initiation of study drug, and have sufficient washout from temozolomide, DRD2 antagonists, strong CYP3A4/5 inhibitors and inducers, and investigational agents. Patients with spinal tumors, DIPG, concurrent malignancy, or prior receipt of whole-brain radiotherapy, proton radiotherapy, ONC201, ONC206, bevacizumab, or tumor-treating fields are not eligible. Complete eligibility criteria are shown in **Table 2**.

Assessments

Patients have study visits every four weeks during cycles 1-12; subsequent visits occur every eight weeks. Where permitted, home health visits may replace an office visit for even numbered cycles through Cycle 12. Disease assessment via contrast-enhanced MRI scans of the

brain occurs approximately every eight weeks (± two weeks) until death, initiation of subsequent anticancer therapy, or withdrawal of consent. PFS endpoints are assessed by blinded, independent central review using a dual reader with adjudication paradigm. Where available, patients provide MRIs conducted prior to radiotherapy. A summary of select study visit assessments is shown in **Table 3**.

Patient tissue samples may be used for correlative biomarker analyses. Blood samples are collected for biobanking and future analysis on Day 1 (pre-dose), C3D1 (± 7 days), and every 8 weeks (± 7 days) thereafter, ideally within 5 days of each scheduled MRI (**Table 3**). When available, formalin-fixed paraffin embedded slides are collected to enable biomarker analyses (**Table 2**).

Statistical Considerations

Approximately 530 patients will be screened and approximately 450 patients will be randomized to achieve 327 OS events and 286 PFS events at each final analysis. The expected true hazard ratio is 0.65 for OS and 0.60 for PFS, with a minimum desired statistical power of 80%. Each primary analysis will independently compare each of the two ONC201 dosing arms with the placebo arm.

Two interim OS analyses are planned following 164 OS events (0.00098 nominal two-sided alpha level) and 246 OS events (0.01064 nominal two-sided alpha level). The final OS analysis, conducted once 327 OS events have been observed, will be performed at a 0.0346 nominal two-sided alpha level. The final PFS analysis will be performed once 286 PFS events

have occurred (0.012 alpha level); no interim PFS analysis is planned. For both PFS and OS analyses, the Hochberg method will be used to account for the 2-dose group comparison.

Study Sites

More than 120 international study sites are targeted in at least 15 countries globally, including centers in North America, Europe, Israel, and Asia-Pacific. Currently open sites can be found at https://clinicaltrials.gov/ct2/show/NCT05580562.

Discussion

With no known effective treatments other than radiation, H3 K27M-mutant diffuse glioma has a dire unmet need for new therapies. ACTION is the largest interventional clinical trial in patients with H3 K27M-mutant diffuse gliomas, and was designed to serve as the basis for regulatory approval of ONC201. The planned enrollment of 450 patients requires international collaboration and support from treating physicians. Transparency for the rationale for the scientific design of clinical trials is vital to collaboration and, as such, we outline the rationale for key aspects of ACTION trial design below.

Inclusion of Only Patients with H3 K27M-mutant Disease

The ACTION trial only enrolls patients who have H3 K27M-mutant diffuse glioma as confirmed by IHC or NGS. To date, responses to ONC201 monotherapy among patients with glioma have been limited to the H3 K27M mutation and therefore the ACTION trial is limited to that population.[19] The definition of H3 K27M-mutant glioma in this protocol reflects guidance from the 2016 WHO classification of CNS tumors.[5] As ACTION is intended as a global registrational trial, it is beneficial to specifically define the patient population, where the mutation has been well-characterized and is part of the standard diagnostic criteria. H3 K27M mutational status is often determined as part of diagnosis, either by IHC or NGS, and there is a high level of concordance between these two testing strategies.[20-25]

The 2021 version of the WHO classification of solid tumors expanded the definition to H3 K27-altered tumors, which is inclusive of other tumors that result in a global loss of H3 K27 tri-methylation due to the H3 K27M mutation or other molecular mechanisms.[6] It is important to note that the H3 K27M mutation accounts for the majority of thalamic and spinal cases of pediatric HGG.[26,27] Furthermore, although one could argue that treatment with ONC201 could benefit these patients by the reversal of H3 K27 trimethyl loss[18], this activity has not yet been evaluated in patients.

Tumor Location

Tumor location is not restricted to the midline for ACTION eligibility, as ONC201 has demonstrated responses in both midline[28] and non-midline diffuse glioma.[29] Primary spinal or pontine tumors are excluded due to competing pediatric studies that were ongoing prior to ACTION. One such trial is PNOC022, a phase 2 trial evaluating ONC201 in combination with other anti-cancer compounds,[30] and the second the phase 3 Biological Medicine for DIPG Eradication 2.0 (BIOMEDE2.0) trial, which is evaluating the efficacy of ONC201 relative to everolimus.[31] As such, excluding DIPG from ACTION ensures a more homogeneous patient population for this potentially registrational trial while also avoiding competition for patients with other important trials in DIPG.

Definition of Standard of Care

Currently, the standard of care for H3 K27M-mutant diffuse glioma is radiotherapy followed by supportive care. Some physicians treat patients with temozolomide due to its activity in molecularly unselected glioblastoma. Additionally, patients treated with temozolomide are permitted to enroll on trial, with a required 3-week washout. However, temozolomide has failed to demonstrate efficacy in patients with H3 K27M-mutant or MGMT-unmethylated high grade glioma.[8,32,33]

ACTION requires that all enrolled patients receive frontline radiotherapy. At first progression and at the physician's discretion, patients may continue on treatment and additionally receive re-irradiation and bevacizumab. Alternatively, any patients may discontinue treatment and pursue other treatments options. This is in line with current standard of care, in which patients are monitored for progression following radiation, after which other treatment options may be considered.

Inclusion of Placebo

ACTION is a placebo-controlled trial that is designed to be a global registrational trial and facilitate regulatory approval. Placebo-controlled studies are the most robust clinical trial design methodology, as it minimizes bias from multiple sources. Placebo ensures compliance within the study, as otherwise an open-label design would be expected to have increased study dropout rates and/or lost-followed that would preclude evaluation.[34]

Inclusion of Two Active Dose Levels

ACTION evaluates two ONC201 dose schedules. The decision to include two dose schedules of ONC201 was based on FDA feedback related to Project Optimus.[35] Furthermore, the randomization that includes to treatment arms ensures that two-thirds of enrolled patients receive ONC201.

Cross-over

Due to the requirement of overall survival as the key regulatory endpoint of ACTION, cross-over is not permitted. This decision was made due to the confounding effects cross-over may have on OS. If an effect on OS becomes apparent only later in disease course, following the time at which most placebo-treated patients cross over, efficacy analyses could be confounded by treatment with the active compound and decrease the chances of a positive trial. In a review of cross-over and non-cross-over oncology studies, OS improvement was observed in 70.2% (33/47) non-cross-over trials, compared with only 25.0% (4/16) of cross-over designs.[36] There have been examples of late-stage trials in high grade gliomas where crossover has confounded the evaluation of overall survival.[37,38] The omission of cross-over from ACTION's design provides the best opportunity for an unconfounded trial and, if successful, ultimately regulatory approval of ONC201. A decision to unblind participants may be considered at the time of a positive planned interim analysis, in conjunction with guidance from regulatory authorities.

Conclusion

Participation in rigorously designed clinical trials is essential for the proper evaluation of novel therapeutics for underserved indications and are required for regulatory authorization. The ACTION trial will assess the safety and efficacy of ONC201 in newly diagnosed patients with H3 K27M-mutant diffuse glioma following radiotherapy and is intended to support regulatory approval in multiple countries if proven effective.

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Conflict of Interest

Isabel Arrillaga-Romany has received research funding Chimerix, Inc. Andrew Lassman has served on advisory board for Chimerix, Inc and received equipment, materials, or medical writing support from Chimerix, Inc. Susan L. McGovern has served on an advisory board for Chimerix, Inc. Sabine Mueller has no relevant conflicts of interest to declare. Burt Nabors has served on an advisory board for Chimerix, Inc. Martin van den Bent has no relevant conflicts of interest to declare. Michael Vogelbaum has served on an advisory board for Chimerix, Inc. Joshua E. Allen, Allen S Melemed, and Rohinton S Tarapore are employees of and have stock ownership in Chimerix, Inc. Joshua E. Allen has patents related to ONC201. Patrick Y Wen has received research funding from Chimerix, Inc., served as a consultant for Chimerix, Inc., and served on an advisory board for Chimerix, Inc. Timothy Cloughesy has received research funding from Chimerix, Inc, owns stock in Chimerix, Inc, and receives milestone payments and possible future royalties from Chimerix, Inc.

Author Contributions

Study Design: IAR, AL, SLM, SM, BN, MvdB, MV, JEA, ASM, RST, PYW, TC

Data Collection: non-applicable

Statistical Analyses: non-applicable

Manuscript Preparation: IAR, JEA, ASM, RST

Manuscript Review: IAR, AL, SLM, SM, BN, MvdB, MV, JEA, ASM, RST, PYW, TC

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Figure Legends.

Figure 1. Study Schematic

C1D1, Cycle 1 Day1; C1D2, Cycle 1 Day 2; MRI, magnetic resonance imaging, Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ONC201 administered following radiotherapy in participants with H3 K27M-mutant diffuse glioma	• OS • PFS using RANO-HGG criteria
Secondary	
To evaluate the safety and tolerability of ONC201 versus placebo	• Incidence of AEs: overall, treatment-related, Grade 3 or higher in severity, serious, fatal, those resulting in treatment discontinuation, and events of special interest • Change from baseline in clinical laboratory parameters • Distribution of graded clinical laboratory parameters
To evaluate the efficacy of ONC201 administered following radiotherapy using RANO-HGG criteria in participants with H3 K27M-mutant diffuse glioma	• PFS using RANO-HGG criteria for participants with measurable contrast-enhancing disease
To evaluate clinical benefits of treatment with ONC201	• Corticosteroid response • Time to first corticosteroid response • Duration of first corticosteroid response • Cumulative duration of corticosteroid responses • Corticosteroid dose and change from baseline over time • Time to corticosteroid use deterioration • Performance status response • Time to first performance status response • Duration of first performance status response • Cumulative duration of performance status responses • Performance status and change from baseline over time • Time to performance status deterioration
To evaluate the impact of ONC201 on health-related QoL and neurological function	• Change from baseline in QoL assessments ○ ≥ 18 years of age: EORTC-QLQ-C30, QLQ-BN20, and MDASI-BT

	○ 2 to < 18 years of age: PedsQL Brain Tumor Module • Change from baseline NANO results
Exploratory	
To assess plasma concentrations and estimate PK parameters for ONC201	• Plasma concentrations of ONC201 • PK parameters for ONC201
To evaluate the exposure-response relationship	• Correlation between extent of exposure to ONC201 and select efficacy and safety endpoints
To evaluate the efficacy of ONC201 using RANO-LGG criteria	• PFS using RANO-LGG criteria
To evaluate the impact of molecular profile on outcomes	• Correlation between the molecular profile of the tumor and efficacy (OS and PFS)
To compare outcomes among selected subgroups	• OS, PFS • Incidence of AEs
To evaluate the impact of ONC201 treatment on health care resource utilization	• Health care resource utilization

AE, adverse events; HGG, high-grade glioma; LGG, low-grade glioma; NANO, Neurologic Assessment in Neuro-Oncology; OS, overall survival; RANO, response assessment in neuro-oncology; PFS, progression-free survival; PK, pharmacokinetic.

Table 2. Eligibility Criteria

Inclusion Criteria
Able to understand the study procedures and agree to participate in the study by providing written informed consent (by participant or legally authorized representative), and assent when applicable.
Body weight ≥ 10 kg at time of randomization.
Histologically diagnosed H3 K27M-mutant diffuse glioma (new diagnosis, nonrecurrent). Detection of a missense K27M mutation in any histone H3-encoding gene detected by local testing of tumor tissue (IHC or NGS in a CLIA-certified or equivalent laboratory). Site to provide (as available): ≥ 10 unstained FFPE slides from tumor tissue
Completed standard frontline radiotherapy (54 to 60 Gy at 1.8 to 2.2 Gy/fraction) ≤ 6 weeks prior to randomization.
At least one, high-quality, contrast-enhanced MRI of the brain obtained prior to starting radiotherapy for submission to sponsor's imaging vendor for central read. For participants who had a surgical resection, this scan must be post-resection; for participants who did not have a resection, this scan may be pre- or post-biopsy.
At least one, high-quality, contrast enhanced MRI of the brain obtained within 2 to 6 weeks after completion of frontline radiotherapy. Site to also provide (if available): pre-surgery/biopsy, post-surgery, and radiation planning MRIs.
KPS/LPS ≥ 70 at time of randomization
Stable or decreasing dose of corticosteroids and anti-seizure medications for 7 days prior to randomization, if applicable. Stable steroid dose is defined as ≤ 2 mg/day increase (based on dexamethasone dose or equivalent dose of alternative steroid).
Exclusion Criteria
Primary spinal tumor.
DIPG, defined as tumors with a pontine epicenter and diffuse involvement of the pons.
Evidence of leptomeningeal spread of disease or CSF dissemination.
Any known concurrent malignancy.

New lesion(s) outside of the radiation field.
Received whole-brain radiotherapy.
Received proton therapy for glioma.
Use of any of the following treatments within the specified time periods prior to randomization: • ONC201 or ONC206 at any time. • Bevacizumab (includes biosimilars) at any time. • Temozolomide within past 3 weeks. • Tumor treating fields at any time. • DRD2 antagonist within past 2 weeks. • Any investigational therapy within past 4 weeks. • Strong CYP3A4/5 inhibitors (see Appendix 8) within 3 days. • Strong CYP3A4/5 inducers (includes enzyme-inducing antiepileptic drugs; see Appendix 8) within 2 weeks.
Laboratory test results meeting any of the following parameters within 2 weeks prior to randomization: • ANC $<1.0 \times 10^9$/L or platelets $<75 \times 10^9$/L. • Total bilirubin >1.5 × ULN (participants with Gilbert's syndrome may be included with total bilirubin >1.5 × ULN if direct bilirubin is ≤1.5 × ULN). • AST or ALT > 2.5 × ULN. • Creatinine clearance ≤ 60 mL/min as calculated by the Cockcroft Gault equation (or estimated glomerular filtration rate < 60 mL/min/1.73 m^2.
QTc >480 msec (based on mean from triplicate ECGs) during screening
Known hypersensitivity to any excipients used in the study intervention formulation.
Pregnant, breastfeeding, or planning to become pregnant while receiving study intervention or within 3 months after the last dose. Participants of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study intervention.

	Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring systemic therapy or psychiatric illness/social situations that would limit compliance with study requirements.
	Any other condition (eg, medical, psychiatric, or social) that, in the opinion of the investigator, may interfere with participant safety or the ability to complete the study according to the protocol.

ANC, Absolute neutrophil count; ALT, alanine aminotransferase alanine aminotransferase; AST, aspartate aminotransferase; CLIA, clinical laboratory improvement amendments; CSF, cerebrospinal fluid; DIPG, diffuse intrinsic pontine glioma; DRD2, dopamine receptor D2; ECG, electrocardiogram; FFPE, formalin-fixed paraffin-embedded; ICH, immunohistochemistry; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status NGS, next-generation sequencing; MRI, magnetic resonance imaging; ULN, upper limit of normal

Table 3. Study Visit Summary of Select Assessments

	Screening (≤ Day -28)	Cycle 1, Day 1	Cycle 1, Day 2	Cycle 2, Day 1	Cycle 3-12 (Q4W)	Cycle ≥13
Weight and height		X		X	X	X
Physical exam/vital signs		X			Cycle 3, Day 1 + Q8W	
12-lead electrocardiogram[a]	X	X	X		Cycle 3, Day 1 + Q8W	
Quality of life questionnaires		X			Cycle 3, Day 1 + Q8W	
Performance status (KPS/LPS)	X	X			Cycle 3, Day 1 + Q8W	
Neurologic exam		X	X		Cycle 3, Day 1 + Q8W	
MRI[b]	X				Cycle 3, Day 1 + Q8W	
Blood collection						
Hematology	X	X		X	X	X
Serum chemistries	X	X		X	X	X
Plasma for exploratory biomarkers/biobanking		X			Cycle 3, Day 1 + Q8W	
Plasma pharmacokinetics		X	X		Cycle 3, Day 1 + Q8W	

[a]Screening electrocardiogram, collect in triplicate (≥ 1 minute intervals); Cycle 1, Day 1 and Cycle 1 Day 2, single tracings predose and between 1 to 2 hours post dose (before pharmacokinetic blood draws); other timepoints, single tracings, predose when applicable. If a tracing indicates QTc prolongation >500 msec, repeat to confirm, then determine if participant requires treatment interruption or discontinuation.

[b]First on-treatment MRI will be collected at C3D1 (± 7 days). Subsequent MRIs will be collected every 8 weeks (± 14 days) while the participant is receiving study intervention and through the time of initiation of a subsequent anticancer therapy. Upon determination of possible radiographic progression per the investigator, a confirmatory scan is required 4 to 10 weeks later.

KPS/LPS, Karnofsky performance score/Lansky performance score; MRI, magnetic resonance imaging

Figure 1