ONC201 (Dordaviprone) in Recurrent H3 K27M–Mutant Diffuse Midline Glioma

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ABSTRACT

PURPOSE Histone 3 (H3) K27M–mutant diffuse midline glioma (DMG) has a dismal prognosis with no established effective therapy beyond radiation. This integrated analysis evaluated single-agent ONC201 (dordaviprone), a first-in-class imipridone, in recurrent H3 K27M–mutant DMG.

METHODS Fifty patients (pediatric, n = 4; adult, n = 46) with recurrent H3 K27M–mutant DMG who received oral ONC201 monotherapy in four clinical trials or one expanded access protocol were included. Eligible patients had measurable disease by Response Assessment in Neuro-Oncology (RANO) high-grade glioma (HGG) criteria and performance score (PS) ≥60 and were ≥90 days from radiation; pontine and spinal tumors were ineligible. The primary end point was overall response rate (ORR) by RANO-HGG criteria. Secondary end points included duration of response (DOR), time to response (TTR), corticosteroid response, PS response, and ORR by RANO low-grade glioma (LGG) criteria. Radiographic end points were assessed by dual-reader, blinded independent central review.

RESULTS The ORR (RANO-HGG) was 20.0% (95% CI, 10.0 to 33.7). The median TTR was 8.3 months (range, 1.9-15.9); the median DOR was 11.2 months (95% CI, 3.8 to not reached). The ORR by combined RANO-HGG/LGG criteria was 30.0% (95% CI, 17.9 to 44.6). A ≥50% corticosteroid dose reduction occurred in 7 of 15 evaluable patients (46.7% [95% CI, 21.3 to 73.4]); PS improvement occurred in 6 of 34 evaluable patients (20.6% [95% CI, 8.7 to 37.9]). Grade 3 treatment-related treatment-emergent adverse events (TR-TEAEs) occurred in 20.0% of patients; the most common was fatigue (n = 5; 10%); no grade 4 TR-TEAEs, deaths, or discontinuations occurred.

CONCLUSION ONC201 monotherapy was well tolerated and exhibited durable and clinically meaningful efficacy in recurrent H3 K27M–mutant DMG.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Histone 3 (H3) K27M mutation is common in diffuse midline glioma (DMG) and associated with a poor median overall survival (OS) of approximately 1 year from diagnosis, though some variability in prognosis may result depending on genotype and age at diagnosis.[1-4,42] As H3 K27M–mutant gliomas are largely restricted to midline brain structures,[4-6] resection is often not possible.[7] Radiotherapy remains the standard of care, no systemic therapies have proven to be effective, and bona fide responses have rarely been reported in the recurrent setting.[8-10] H3 K27M is a dominant negative gain-of-function mutation resulting in sequestration of polycomb repressive complex 2, suppression of histone methyltransferase activity, and a global reduction in trimethylation of H3 at position 27 (H3 K27me3).[11,12] H3 K27M is an initiating oncogenic event in diffuse intrinsic pontine gliomas (DIPG), which is retained in all tumor cells and present throughout the course of the disease; subsequent studies have inferred involvement of a similar precursor cell and molecular biology in DMG.[13-15] As a highly clonal, disease-initiating

CONTEXT

Key Objective

Are there any medications that have shown single-agent activity in patients with recurrent histone 3 (H3) K27M–mutant diffuse midline gliomas?

Knowledge Generated

ONC201 demonstrated single-agent responses by blinded independent review in a highly refractory patient population consisting of patients who had postradiation therapy in the second- or third-line setting. Twenty percent of patients had a response by Response Assessment in Neuro-Oncology high-grade glioma criteria (95% CI, 10.0 to 33.7), and the responses were very durable, with a median duration of response of 11.2 months (95% CI, 3.8 to not reached). ONC201 was well-tolerated; the most common grade 3 or higher treatment-related adverse event was fatigue (10%).

Relevance *(J.P.S. Knisely)*

Clinical relevance is documented in this analysis that showed both clinical and radiographic responses in a pooled analysis of data from five separate clinical trials of ONC-201 (dordaviprone) as a monotherapy in patients with recurrent or progressive contrast-enhancing and measurable H3K27M diffuse midline gliomas outside the brainstem. Active systemic agents are needed for this condition, and ONC-201 is a leading candidate for further study.*

*Relevance section written by *JCO* Associate Editor Jonathan P.S. Knisely, MD.

mutation, H3 K27M may provide a vulnerability for targeted therapy.

ONC201 (dordaviprone) is an oral, blood-brain barrier penetrant, 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).[16-20] Both DRD2/3 and ClpP have been suggested to play a role in gliomas. DRD2 is overexpressed in multiple cancers, including glioblastoma where it was required for tumor growth in vivo and linked to a poor prognosis.[21-24] Ex vivo studies of samples of patients with H3 K27M–mutant glioma have reported overexpression of DRD2 by RNA-seq when maintained in 3D culture.[25] ClpP is upregulated in some malignancies, and its role in the anticancer effects of ONC201 has been shown in several tumor types, including H3 K27M–mutant glioma.[19,26,27] Previous work has suggested that ONC201 hyperactivates ClpP, leading to selective degradation of mitochondrial proteome components and subsequent activation of the integrated stress response and apoptosis.[28] Downstream mitochondrial effects of ONC201 include altered tumor cell metabolism resulting in reversal of pathognomonic loss of H3 K27me3 in H3 K27M–mutant glioma cells.[29] Single-agent ONC201 has shown antitumor efficacy in preclinical in vivo brain tumor models, including H3 K27M–mutant glioma.

A phase II clinical study of ONC201 was conducted in recurrent glioblastoma and included a surgical cohort, which confirmed therapeutic intratumoral concentration of ONC201 with robust pharmacodynamic engagement. Tumor regression was observed exclusively in patients with glioblastoma who incidentally exhibited the H3 K27M mutation.[30,31] A subsequent series of open-label adult and pediatric studies have reported anecdotal clinical benefit in patients with progressive H3 K27M–mutant glioma who received single-agent ONC201,[30-32] and ONC201-treated patients with H3 K27M–mutant DMG had encouraging clinical outcomes.[29]

Once weekly ONC201 administration was well-tolerated, with no dose-limiting toxicities.[30,33,34] The present integrated analysis of five open-label studies was performed to determine the safety and efficacy of ONC201 in patients with recurrent, nonpontine, and nonspinal H3 K27M–mutant DMG.

METHODS

Patients

This integrated analysis included patients from five clinical studies of ONC201 (Appendix Table A1, online only). The rationale for combining the five studies with rigorous selection and blinded assessment was arrived at after discussion with the US Food and Drug Administration (FDA) to produce a sufficiently large population of patients with H3 K27M–mutant DMG, such that a resultant signal would provide meaningful safety and efficacy data. The FDA also provided guidance on the prespecified eligibility criteria used to identify the 50 patients required for this analysis. Patients were assessed by blinded independent centralized review (BICR), with objective response rate according to Response Assessment in Neuro-Oncology-HGG (RANO-HGG) criteria as a primary end point.[35] All studies were approved by institutional review boards, and patients provided written informed consent. Patients initiating ONC201 treatment on or before February 27, 2020, were evaluated for eligibility.

Eligible patients had recurrent and/or progressive H3 K27M–mutant glioma that was measurable per RANO-HGG, were 2 years and older, had a Karnofsky/Lansky performance score (KPS/LPS) of ≥60, and received previous radiation therapy (RT) with a washout of ≥90 days before first ONC201 dose, which was included to reduce the likelihood of enrolling patients with pseudoprogression, per RANO guidance. Patients were on a stable or decreasing dosage of corticosteroids for at least 3 days before baseline scan, and patients were excluded if they had DIPG, leptomeningeal spread, CSF dissemination, or a primary spinal tumor, given the difficulty of measuring responses in these tumors by RANO-HGG criteria (Appendix Table A2). H3 K27M status was confirmed by immunohistochemistry or sequencing in a Clinical Laboratory Improvement Amendments (CLIA) or equivalent setting.

Treatment

Adults (18 years and older) received open-label ONC201 (625 mg) as oral capsules (125 mg/capsule). For pediatric patients, the adult dose (625 mg) was allometrically scaled by body weight, calculated using a power model assuming an average adult weight of 70 kg and an exponent of three fourth, and rounded to the nearest capsule dose. Frequency of administration (once weekly or once every 3 weeks) and treatment cycle length (3-4 weeks) depended on study design (Appendix Table A1). Patients were treated at least until progression by investigator-assessed RANO-HGG criteria.

Assessments

Magnetic resonance images (MRIs; T1-, T2-, or Fluid-Attenuated Inversion Recovery [FLAIR]–weighted images) were obtained at baseline and every 8 weeks after treatment initiation. Since not all midline gliomas uniformly enhance, radiographic assessment included RANO-HGG[35] and RANO-Low-Grade Glioma (RANO-LGG)[36] Criteria, by dual-reader BICR; response assessment for all patients in the present analysis was uniform, regardless of the contributing trial in which the patient was enrolled. At the beginning of each cycle, KPS/LPS and concomitant medications, including changes in total daily corticosteroid dosage, were assessed. Adverse events were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0 or 5.0, depending on the trial; Appendix Table A1).

Statistical Analysis

The last eligible patient was enrolled on February 27, 2020. Cutoff dates were May 31, 2021, for efficacy and December 31, 2021, for safety. The planned sample size was 50, which would exclude a lower 95% CI boundary of <10% with an observed 20% response rate by RANO-HGG. The primary end point was overall response rate (ORR) by RANO-HGG according to the BICR (complete response [CR] and partial response [PR]).[35] Secondary end points included ORR by RANO-LGG criteria (CR, PR and minor response [MR]),[36] duration of response (DOR), time to response (TTR), best overall response, disease control rate (DCR), progression-free survival (PFS), OS, corticosteroid response rate, and performance score (PS) response rate. CIs for DOR were determined with an exact CI. PFS was defined as time from treatment initiation to documentation of PD (RANO-HGG) or death. OS was defined as time from ONC201 treatment initiation until death. PFS and OS curves were generated using

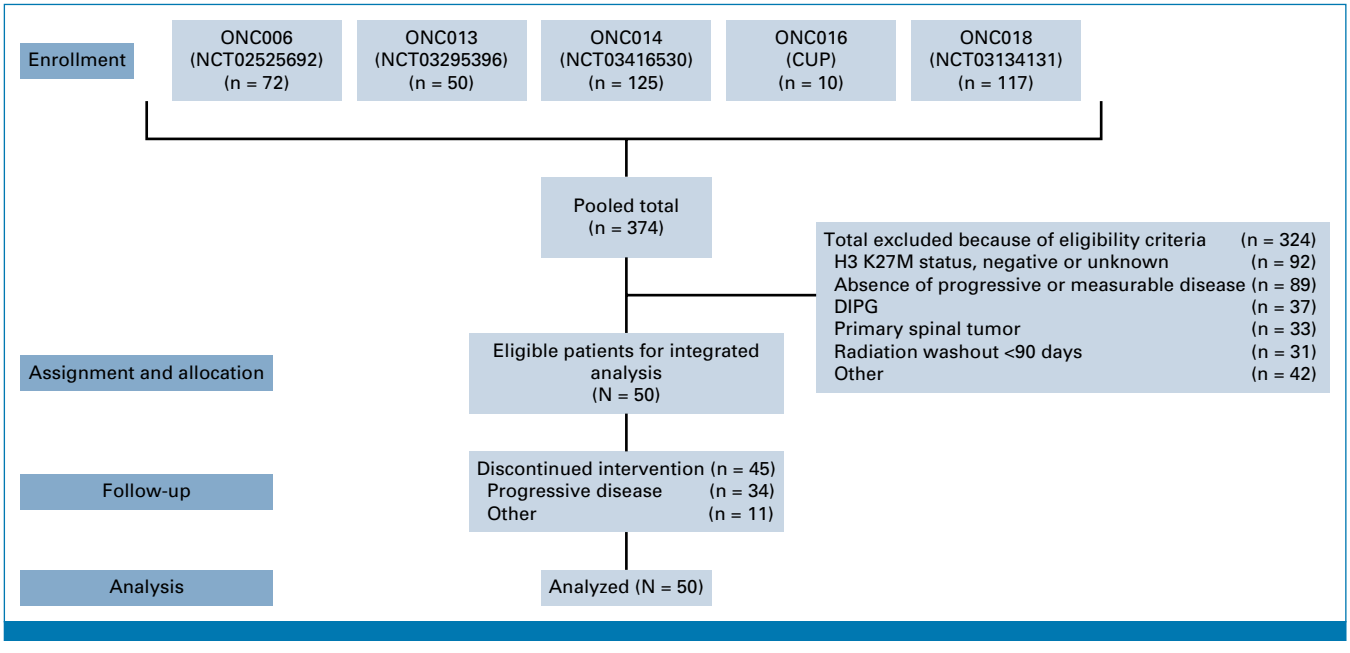

FIG 1. CONSORT diagram. CUP, compassionate use program; DIPG, diffuse intrinsic pontine glioma.

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	All Patients (N = 50)
Age, years, median (range)	30 (8-70)
<18, No. (%)	4 (8)
18 to <40, No. (%)	32 (64)
≥40, No. (%)	14 (28)
Sex, No. (%)	
Male	27 (54.0)
Female	23 (46.0)
Race, No. (%)	
White	39 (78.0)
Other	6 (12.0)
Black	3 (6.0)
Asian	1 (2.0)
Unknown	1 (2.0)
Body weight, kg, median (range)	88 (29-199)
Performance score (KPS/LPS), No. (%)	
60	7 (14.0)
70	7 (14.0)
80	20 (40.0)
90	14 (28.0)
100	2 (4.0)
Primary tumor location, No. (%)	
Thalamic	33 (66.0)
Other midline	17 (34.0)
Multifocal disease,[a] No. (%)	23 (46.0)
More than one target lesion, No. (%)	9 (18.0)
Tumor size, cm^2, median (range)	10.4 (1.6-40.8)
H3 K27M detection method, No. (%)	
IHC	47 (94.0)
NGS	3 (6.0)
First recurrence, No. (%)	37 (74.0)
Previous temozolomide, No. (%)	44 (88.0)
Time from recurrence, days, median (range)	20 (1-126)
Time from previous radiation, months, median (range)	7.5 (3-104)
Time from initial diagnosis, months, median (range)	10.9 (5-105)
Daily steroid dose (daily dexamethasone equivalent dose), mg, median (range)	1.1 (0.0-12.0)

Abbreviations: BICR, blind independent central review; IHC, immunohistochemistry; KPS, Karnofsky performance score; LPS, Lansky performance score; NGS, next-generation sequencing.
[a]Multifocal disease includes nontarget lesions.
[b]Sum of product of diameters of enhancing target lesions per BICR.

the Kaplan-Meier method. CIs for PFS and OS were estimated from Kaplan-Meier analysis. Patients were censored for all end points, except OS, on initiation of any additional anticancer therapy.

For analysis of improved KPS/LPS, evaluable patients had a KPS/LPS of ≤80 at baseline; responders had a confirmed increase from baseline KPS/LPS with stable/reduced corticosteroid use. For analysis of decreased corticosteroid use, evaluable patients had a cumulative daily dose of ≥4 mg dexamethasone equivalent dose at baseline, which was administered once daily at 4 mg per dose or twice daily at 2 mg per dose; responders had a confirmed ≥50% reduction from baseline in average daily corticosteroid dose with stable or improved KPS/LPS. Both KPS/LPS and corticosteroid responses were confirmed if the patient met the required parameters at their next study visit (approximately 8 weeks later). ORR subgroup analyses by baseline characteristics included age (<18, 18-<40, or ≥40 years), race (White or other), ethnicity (Hispanic/Latino, not Hispanic/Latino, or unknown), sex (female or male), PS (60, 70, 80, 90, or 100), weight (<55 or ≥55 kg), primary tumor location (non-thalamus or thalamus), multifocal disease (yes or no), tumor size (<10 or ≥10 cm^2), number of target lesions (<2 or ≥2), H3 K27M assay (immunohistochemistry or next-generation sequencing), H3 K27M histone (H3.1, H3.3, or unknown), days from recurrence (<21 or ≥21), number of recurrences (1, 2, or 3), reirradiation (yes or no), and steroid use at baseline (0, 0 to <4, or ≥4 mg daily dexamethasone equivalent dose).

Role of the Funding Source

The sponsor of relevant clinical studies was Chimerix, Inc, which provided funding for all studies included in this analysis (ClinicalTrials.gov identifiers: NCT02525692, NCT03295396, NCT03416530, NCT03134131 and the compassionate use program). Chimerix, Inc helped develop the study design, monitored study conduct and data collection, performed data analyses, and supported the writing of the manuscript. A National Cancer Institute SBIR Bridge grant (grant 2R44CA192427-04) supported the conduct of ONC006 (ClinicalTrials.gov identifier: NCT02525692) and ONC013 (ClinicalTrials.gov identifier: NCT03295396). The Making Headway Foundation provided support for ONC018 (ClinicalTrials.gov identifier: NCT03134131). The Fly a Kite Foundation provided support for ONC014 (ClinicalTrials.gov identifier: NCT03416530) at the New York University, Grossman School of Medicine study site.

RESULTS

Patients

Patients who received their first dose of ONC201 on or between March 31, 2016, and February 26, 2020, and met the prespecified eligibility for efficacy analysis were evaluated. The most common reasons for exclusion were negative or unknown H3 K27M status (n = 92), the absence of progressive or measurable disease (n = 89), primary spinal tumor (n = 33), and inadequate RT washout (n = 31; Fig 1; Appendix Figs A1-A5).

Most patients were adults (median age, 30 years; range, 8-70); 64% (n = 32) were 18 to <40 years old (Table 1). The most common tumor location was the thalamus (n = 33; 66%). Most patients enrolled after their first recurrence (n = 37; 74%) and

TABLE 2. ORR

Parameter	Efficacy Population (N = 50)		
	RANO-HGG[a]	RANO-LGG[b]	Combined HGG/LGG[c]
ORR, No. (%) [95% CI]	10 (20.0) [10.0 to 33.7]	13 (26.0) [14.6 to 40.3]	15 (30.0) [17.9 to 44.7]
CR	1 (2.0)	0	1 (2.0)
PR	9 (18.0)	6 (12.0)	9 (18.0)
MR	NA	7 (14.0)	5 (10.0)
SD	10 (20.0)	8 (16.0)	7 (14.0)
NE	8 (16.0)[d]	11 (22.0)[e]	11 (22.0)
PD	18 (36.0)	14 (28.0)	13 (26.0)
NA	4 (8.0)[f]	4 (8.0)[f]	4 (8.0)[f]
DCR, No. (%) [95% CI]	20 (40.0) [26.4 to 54.8]	21 (42.0) [28.2 to 56.8]	22 (44.0) [30.0 to 58.7]

Abbreviations: BICR, blind independent central review; CR, complete response; DCR, disease control rate (CR + PR + SD); HGG, high-grade glioma; LGG, low-grade glioma; MR, minor response; MRI, magnetic resonance imaging; NA, not applicable; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease.

[a]Integrated RANO-HGG criteria assessment by dual-reader BICR.

[b]Integrated RANO-LGG criteria assessment by dual-reader BICR.

[c]Incorporates the best response by RANO-HGG or RANO-LGG criteria for each patient.

[d]Five overall radiographic SD accompanied by increase in corticosteroids; three overall radiographic PD accompanied by decrease in corticosteroids.

[e]Eight overall radiographic SD accompanied by increase in corticosteroids; three overall radiographic PD accompanied by decrease in corticosteroids.

[f]Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored before first on-treatment MRI.

received previous temozolomide (n = 44; 88%). The median time from completion of radiotherapy to ONC201 initiation was 7.5 months (range, 3.0-103.6). Except for one patient who received ONC201 once every 3 weeks, all patients received once-weekly ONC201. The median duration of follow-up was 18.8 months. Five patients remained on ONC201 treatment as of the efficacy analysis cutoff date; of these, four were continuing with study treatment after disease progression.

Efficacy

The ORR by RANO-HGG was 20% (95% CI, 10.0 to 33.7), including one CR and nine PRs (Table 2 and Fig 2), and the DCR was 40% (95% CI, 26.4 to 54.8; SD, n = 10). The median DOR was 11.2 months (95% CI, 3.8 to not reached), and the median TTR was 8.3 months (range, 1.9-15.9; Fig 2). The PFS by RANO-HGG at 6 months was 35.1% (95% CI, 21.2 to 49.3; Appendix Fig A6). The median OS was 13.7 months (95% CI, 8.0 to 20.3); 12- and 24-month OS rate were 57.3% (95% CI, 41.4 to 70.3) and 34.7% (95% CI, 20.7 to 49.2), respectively (Appendix Fig A7).

When assessed by RANO-LGG criteria, the ORR was 26.0% (95% CI, 14.6 to 40.3), including six PRs and seven MRs; the DCR by RANO-LGG was 42.0% (95% CI, 28.2 to 56.8; SD, n = 8; Table 2 and Appendix Fig A8). When summarized using the best response by either RANO-HGG or RANO-LGG criteria, the ORR was 30.0% (95% CI, 17.9 to 44.6), which included one CR, nine PRs, and five MRs; the DCR was 44.0% (95% CI, 30.0 to 58.7; SD, n = 7; Table 2). Baseline characteristics and response parameters of responders are shown in Appendix Table A3.

The corticosteroid response rate among 15 evaluable patients was 46.7% (7 of 15; 95% CI, 21.3 to 73.4); the median time to corticosteroid response was 3.7 months (range, 1.9-5.6; Appendix Table A4). The KPS/LPS response rate among 34 evaluable patients was 20.6% (7 of 34; 95% CI, 8.7 to 37.9). The median time to KPS/LPS response was 3.5 months (range, 1.9-22.4; Appendix Table A4).

Subgroup analyses of ORR (RANO-HGG) in groups stratified by age, race, sex, weight, primary tumor location, multifocal disease, tumor size, days from recurrence, and steroid use at baseline were largely comparable between subgroups (Table 3); however, the ORR in patients with a PS of 60 (0 of 7) or 70 (1 of 7, 14.3%) was lower compared with patients with a score of 80 (4 of 20, 20.0%), 90 (4 of 14, 28.6%), or 100 (1 of 2, 50.0%). No patients with two or more target lesions had a response by RANO-HGG criteria to ONC201 treatment (0 of 9) although neither multifocal disease nor overall tumor size demonstrated an obvious trend with objective response. Tumor response by PS at baseline is shown in Appendix Figure A9. The median time from completion of previous RT to ONC201 initiation among patients who achieved an objective response by RANO-HGG criteria was 5.5 months (range, 3.0-9.1).

Safety

All but one patient experienced at least one treatment-emergent adverse event (TEAE); the most common were fatigue (n = 23, 46.0%), nausea (n = 18, 36%), and headache (n = 16, 32.0%; Appendix Table A5). Treatment-related

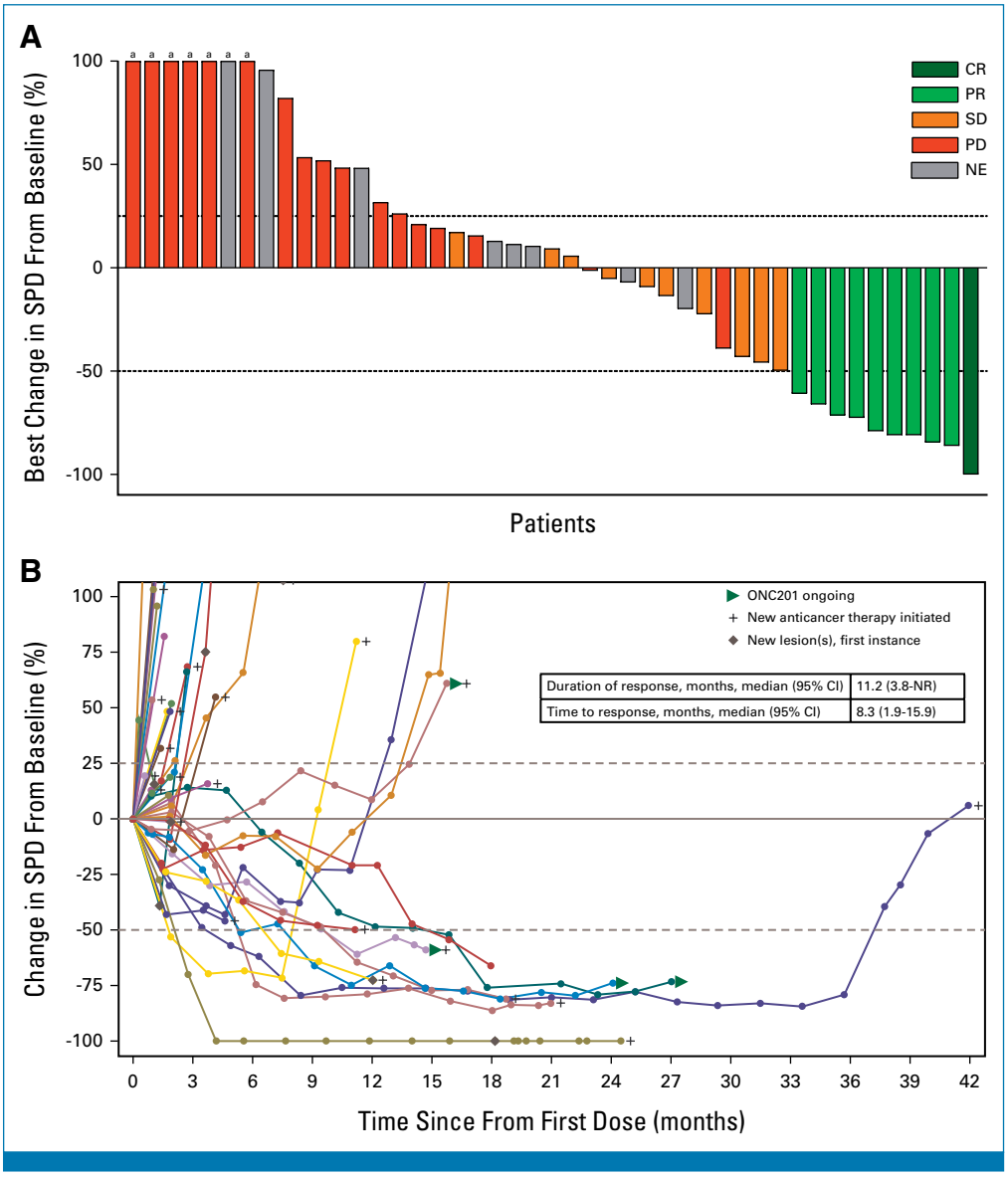

FIG 2. Change in tumor size by RANO-HGG criteria in the efficacy population. (A) Swimmer and (B) spider plots of patients in the efficacy population assessed by BICR while receiving monotherapy ONC201. Three patients did not have on-treatment MRIs available for BICR; one patient censored before first on-treatment MRI because of concurrent therapy; one patient did not have measurable target lesion by BICR. [a]Change >100%. BICR, blinded independent centralized review; CR, complete response; MRI, magnetic resonance imaging; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of products of perpendicular diameters (target-enhancing lesions per BICR).

TEAEs (TR-TEAEs) occurred in 60.0% (n = 30) of patients, including fatigue (n = 16; 34.0%), nausea (n = 9; 18.0%), and decreased lymphocyte count (n = 14; 14.0%; Table 4). Most patients experienced a maximum severity of grade 1-2 (n = 20); among 10 patients who had a grade 3 TR-TEAE, the only TR-TEAE occurring in >2 patients was fatigue (n = 5; 10.0%). No grade 4 TR-TEAEs or treatment-related deaths occurred.

Serious adverse events (SAEs) occurred in 23 patients (46.0%); the most common were hydrocephalus and nausea (each n = 4, 8.0%; Appendix Table A6). There were no SAEs that were considered related by the sponsor although two patients had an SAE that was considered possibly related by the investigator. This included one patient with a seizure and one patient with a pulmonary embolism. The seizure event occurred in September 2021, after 22 months of continuous ONC201 treatment and through multiple radiographic determinations of progressive disease. The patient had a history of seizures and continuous ONC201 without dose reduction/interruption or subsequent seizures. The patient with the pulmonary embolism had significant underlying

TABLE 3. Overall Response Rate by Response Assessment in Neuro-Oncology High-Grade Glioma in Baseline Characteristic Subgroups

Subgroup Analysis	Total Patients in Subgroup (N = 50), No.[a]/No.[b] (%)
Age, years	
<18	1/4 (25.0)
18 to <40	5/32 (15.6)
≥40	4/14 (28.6)
Race	
White	8/39 (20.5)
Other	2/11 (18.2)
Ethnicity	
Hispanic or Latino	1/4 (25.0)
Not Hispanic or Latino	7/41 (17.1)
Unknown	2/5 (40.0)
Sex	
Female	4/23 (17.4)
Male	6/27 (22.2)
Performance score	
60	0/7 (0)
70	1/7 (14.3)
80	4/20 (20.0)
90	4/14 (28.6)
100	1/2 (50.0)
Weight, kg	
<55	1/6 (16.7)
≥55	9/44 (20.5)
Primary tumor location	
Nonthalamus	2/17 (11.8)
Thalamus	8/33 (24.2)
Multifocal disease[c]	
No	6/27 (22.2)
Yes	4/23 (17.4)
Tumor size, cm^{2}[c]	
<10	5/22 (22.7)
≥10	5/27 (18.5)
Unknown/missing/NA	0/1 (0)
No. of target lesions[c]	
<2	10/41 (24.4)
≥2	0/9 (0)
H3 K27M assay	
IHC	9/47 (19.1)
NGS	1/3 (33.3)
H3 K27M histone	
H3.1	1/1 (100.0)
H3.3	0/2 (0)
Unknown	9/47 (19.1)
Days from recurrence	
<21	6/26 (23.1)
≥21	4/24 (16.7)
No. of recurrences	
1	8/37 (21.6)
2	2/11 (18.2)
3	0/2 (0)

(continued on following page)

TABLE 3. Overall Response Rate by Response Assessment in Neuro-Oncology High-Grade Glioma in Baseline Characteristic Subgroups (continued)

Subgroup Analysis	Total Patients in Subgroup (N = 50), No.[a]/No.[b] (%)
Previous reirradiation[d]	
No	10/47 (21.3)
Yes	0/3 (0)
Steroid use (dexamethasone equivalent), mg daily	
0	4/21 (19.0)
0 to <4	2/14 (14.3)
≥4	4/15 (26.7)

Abbreviations: BICR, blind independent central review; IHC, immunohistochemistry; NA, not available; NGS, next-generation sequencing.
[a]Number of patients with a response.
[b]Number of patients in individual subgroups.
[c]Per BICR, multifocal disease based on the number of target- and non–target-enhancing lesions.
[d]Reirradiation, and progression subsequent to reirradiation, occurred before study entry/ONC201 initiation.

comorbidities including obesity and hypertension and continued on ONC201 at a reduced dose after the embolism for an additional 7 months without further SAEs. TEAEs leading to discontinuation, reduction, or interruption occurred in four (8.0%) patients (Appendix Table A7). No discontinuations occurred because of TR-TEAE. Dose reduction/interruption because of a TR-TEAE occurred in one patient (2.0%) because of the pulmonary embolism discussed above.

DISCUSSION

In this integrated analysis of patients from five clinical studies, ONC201 monotherapy exhibited durable and clinically meaningful efficacy in recurrent, H3 K27M–mutant DMG. By RANO-HGG criteria, the ORR was 20% (95% CI, 10.0 to 33.7) and the DOR was 11.2 months (3.8-not reached). While the median TTR (RANO-HGG) was 8.3 months (range, 1.9-15.9), other measures of clinical benefit occurred earlier, including corticosteroid responses (median TTR, 3.7 months; range, 1.9-5.6) and KPS/LPS response (median TTR, 3.5; range, 1.9-22.4), suggesting that clinical benefit was apparent before patients achieved an objective response.

A recent pooled analysis of a pediatric clinical trial (ClinicalTrials.gov identifier: NCT03416530) and an expanded access protocol (ClinicalTrials.gov identifier: NCT03134131) evaluated clinical outcomes in 71 patients with H3 K27M–mutant DMG, of whom five overlapped with the present analysis.[29] Unlike the present analysis, analyses by Venneti et al[29] were inclusive of patients treated before disease

TABLE 4. TR-TEAEs Occurring in ≥5% of Patients

	All Patients (n = 50), No. (%)			
TR-TEAE	Grade 1	Grade 2	Grade 3	All Grades
Patients with at least one TR-TEAE	10 (20.0)	10 (20.0)	10 (20.0)	30 (60.0)
Fatigue	7 (14.0)	5 (10.0)	5 (10.0)	17 (34.0)
Nausea	8 (16.0)	1 (2.0)	0	9 (18.0)
Lymphocyte count decreased	2 (4.0)	4 (8.0)	1 (2.0)	7 (14.0)
Headache	3 (6.0)	1 (2.0)	1 (2.0)	5 (10.0)
Vomiting	5 (10.0)	0	0	5 (10.0)
Anemia	2 (4.0)	1 (2.0)	0	3 (6.0)
Decreased appetite	1 (2.0)	2 (4.0)	0	3 (6.0)
Dizziness	3 (6.0)	0	0	3 (6.0)
Fall	2 (4.0)	1 (2.0)	0	3 (6.0)
Hemiparesis	1 (2.0)	2 (4.0)	0	3 (6.0)
Rash maculopapular	1 (2.0)	0	2 (4.0)	3 (6.0)

Abbreviations: TR-TEAE, treatment-related treatment-emergent adverse event.

recurrence, did not require response-evaluable disease according to RANO-HGG criteria, and did not impose unifying inclusion criteria for washout from previous therapies, including radiation, and response assessment was conducted by the investigator rather than BICR. The median OS from diagnosis was 21.7 for ONC201-treated patients versus 12 months among external controls. Mechanistic investigations revealed that ONC201 reverses loss of H3 K27me3 in H3 K27M–mutant glioma models and autopsy samples obtained from treated patients.

Outcomes in the present analysis are particularly important in DMG, where survival is typically short and no effective systemic treatments are available. To our knowledge, centrally confirmed objective responses to monotherapy have not been previously reported by integrated RANO-HGG criteria in patients with H3 K27M–mutant DMG, without confounding factors such as RT and bevacizumab. It is notable that a majority of patients in this analysis (n = 44, 88.0%) received previous temozolomide; this is despite the predominance of unmethylated *MGMT* promoter in H3 K27M–mutant glioma, lack of demonstrated efficacy of temozolomide in H3 K27M–mutant DMG, and a negative efficacy outcome for temozolomide in a DIPG clinical trial.[37-40] This is likely because combination of RT and temozolomide, which previously demonstrated efficacy in molecularly unselected, newly diagnosed glioblastoma, is commonly used despite lack of clear evidence of efficacy in this indication.[41] Together, these factors underscore the need for novel treatments of H3 K27M–mutant glioma.

Responses by RANO-HGG and RANO-LGG criteria in the present analysis were largely consistent, indicating that therapeutic benefit was observed in both enhancing and nonenhancing lesions. The presence of responses by both RANO-HGG and RANO-LGG criteria in multiple patients suggests that these responses are authentic. While the impact of pseudoprogression cannot be definitively excluded, the protracted time from previous RT to ONC201 initiation, which exceeds the 90-day guidance from RANO criteria, and the delayed onset and durability of response diminish the likelihood that pseudoprogression accounts for all observed responses. This is further supported by the selective efficacy of ONC201 among patients with H3 K27M–mutant glioma as no responses, genuine or otherwise, were observed in concurrently enrolled patients with H3 wild-type supratentorial glioblastoma.[30,31] Future work is needed to definitively exclude the impact of pseudoprogression in this patient population.

While most subgroup analyses suggested that the efficacy of ONC201 is agnostic to many factors, several appeared to have an inverse relationship with likelihood of response (eg, poor performance score and multiple target lesions). These factors should be considered for eligibility criteria in future clinical studies and suggest that the efficacy of ONC201 may be improved in earlier treatment settings. The relatively slow onset of response also suggests that evaluation in the frontline setting, where PFS is prolonged relative to the recurrent setting, may permit increased duration of therapy and potential benefit.

ONC201 monotherapy was well-tolerated; treatment-related SAEs were uncommon, occurring in two (4.0%) patients. While investigators characterized these two SAEs as possibly related to treatment, these were considered unlikely related to treatment by the sponsor. There were no treatment-related deaths or discontinuations. This safety profile suggests that ONC201 could be well suited to be combined with other therapies or evaluated at more intense dose schedules.

While the five studies from which patients were included had similar design and eligibility criteria, all patients in this analysis had recurrent, measurable, contrast-enhancing H3 K27M–mutant DMG and met unifying criteria for PS status and previous radiotherapy treatment; therefore, the population analyzed here does not reflect the majority of variations that may otherwise be imposed by differences in the eligibility criteria of the contributing trials. The design of this analysis was planned per input from regulatory authorities to objectively assess response to single-agent ONC201 using the most robust assessment methodology (RANO-HGG), without potential confounding by other treatments. Because of the urgency of unmet need in this population and the relative rarity of cases in the general population, an integrated analysis was considered the most expedient method to evaluate ONC201 in these patients.

A limitation of this trial is that as a pooled analysis of uncontrolled trials, these data are not derived from a randomized, placebo-controlled trial and, therefore, it is inherently challenging to interpret PFS and OS results; unlike glioblastoma, H3 K27M–mutant DMG is a relatively recently defined disease subset and, thus, has limited historical data to which the present data can be compared. Another limitation of this trial is that the majority of patients (47 of 50, 94.0%) were confirmed to have H3 K27M–mutant by IHC, which does not discriminate between mutations in *H3.1* and *H3.3* genotypes. Previous research has suggested that genotype may affect OS, with pediatric patients experiencing a shorter OS when the *H3.3* gene is affected, whereas this may confer a prolonged OS in adult patients.[1]

The present analysis also has a bias toward representation of young adult over pediatric patients. This is due to several factors. First, eligible patients were included as they enrolled in their corresponding studies until a cap of 50 patients total was met. The adult studies began enrolling before pediatric studies, potentially contributing to this bias. Second, cases of DIPG, most commonly found in pediatric patients,[43] were excluded from this analysis because of the difficulty in evaluating these tumors by RANO-HGG criteria. Third, unlike the adult trials, the pediatric trial did not require

disease recurrence or a 90-day washout period for RT, thereby severely limiting the number of pediatric patients who would meet eligibility criteria for this analysis.

With no effective therapies beyond RT, H3 K27M–mutant DMG has a poor prognosis.[44] Further research to establish the efficacy of ONC201 in H3 K27M–mutant diffuse gliomas is warranted, and a phase II study of single-agent ONC201 in newly diagnosed H3 K27M–mutant diffuse gliomas is currently enrolling (ClinicalTrials.gov identifier: NCT05580562). In addition, the expanded 2021 WHO disease definition suggests that evaluation of ONC201 in patients with H3 K27me3 loss, without the presence of the H3 K27M mutation, may be warranted.

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ONC201 (Dordaviprone) in Recurrent H3 K27M–Mutant Diffuse Midline Glioma

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APPENDIX

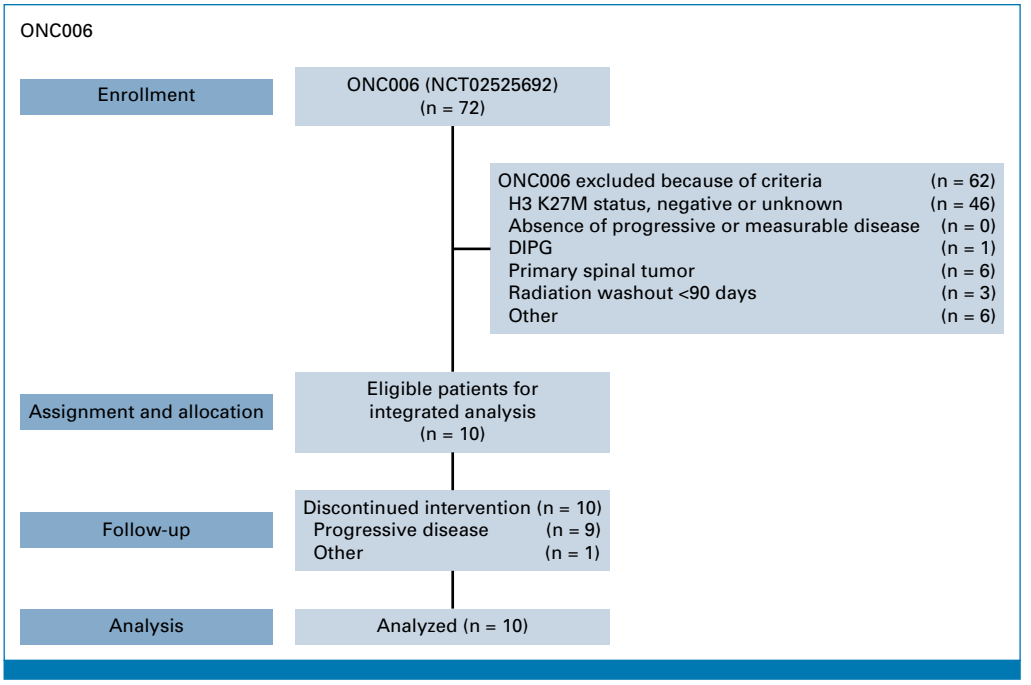

FIG A1. ONC006 CONSORT diagram. DIPG, diffuse intrinsic pontine glioma; H3, histone 3.

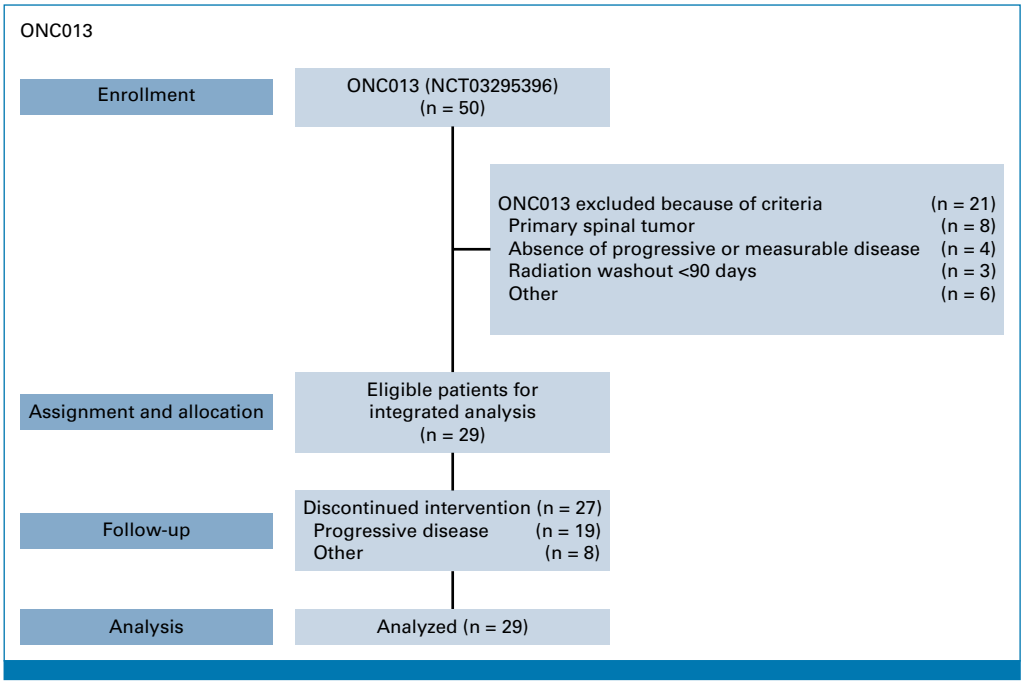

FIG A2. ONC013 CONSORT diagram. DIPG, diffuse intrinsic pontine glioma; H3, histone 3.

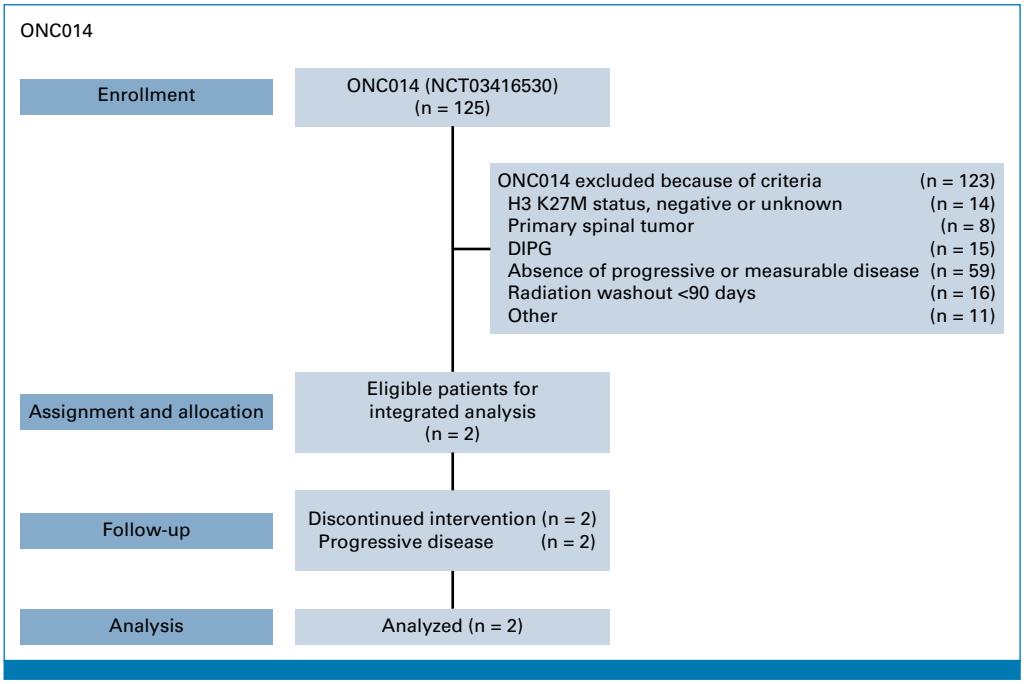

FIG A3. ONC014 CONSORT diagram. DIPG, diffuse intrinsic pontine glioma; H3, histone 3.

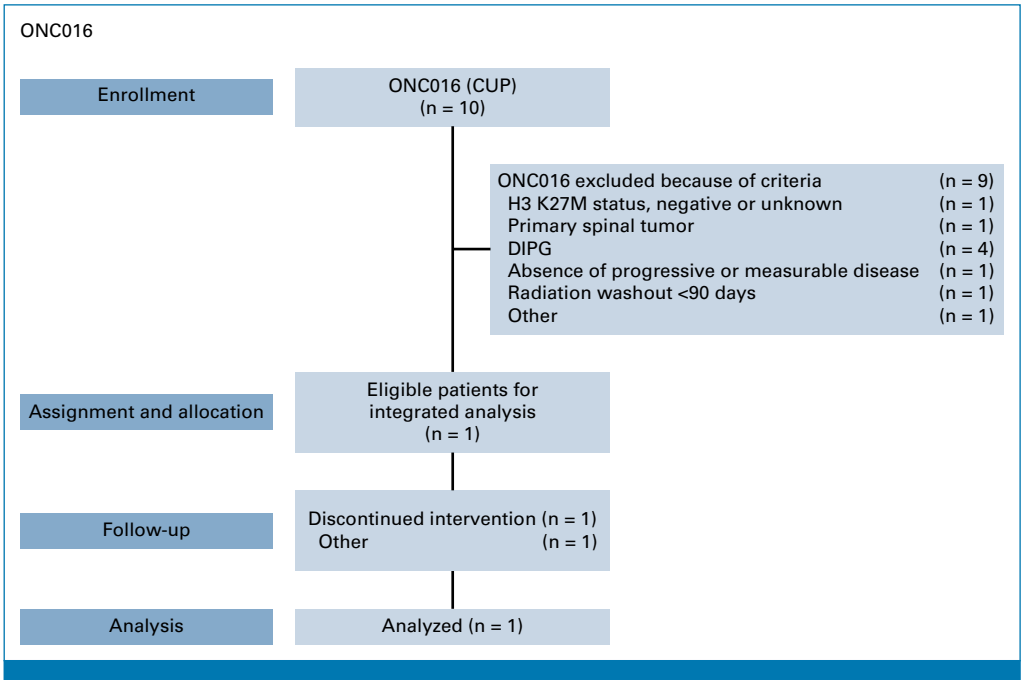

FIG A4. ONC016 CONSORT diagram. CUP, compassionate use program; DIPG, diffuse intrinsic pontine glioma; H3, histone 3.

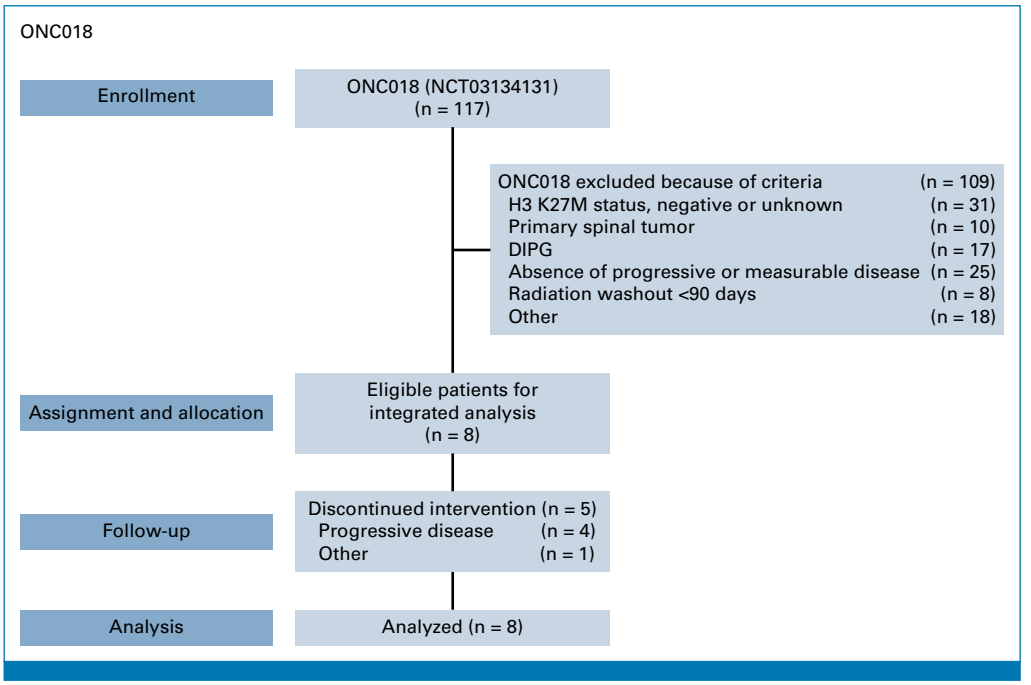

FIG A5. ONC018 CONSORT diagram. DIPG, diffuse intrinsic pontine glioma; H3, histone 3.

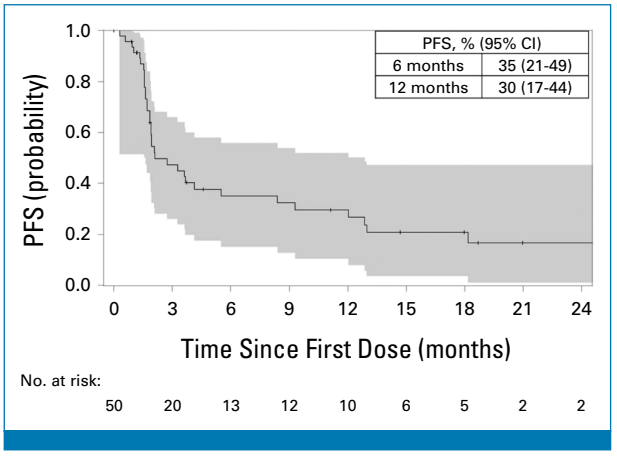

FIG A6. PFS by RANO-HGG in the efficacy analysis population (n = 50). PFS, progression-free survival; RANO-HGG, response assessment in neuro-oncology high-grade glioma. Shaded areas indicate 95% CI.

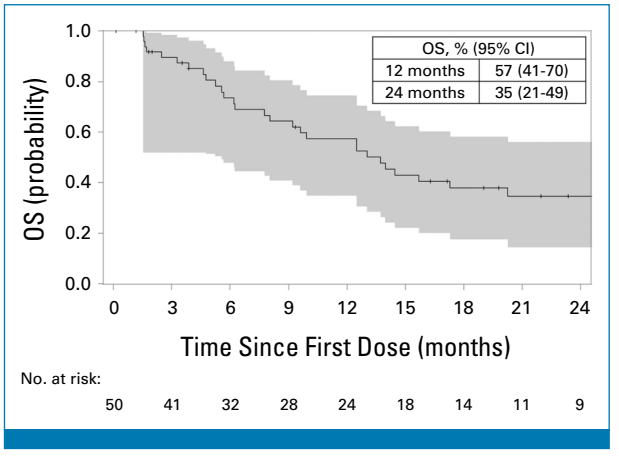

FIG A7. OS in the efficacy analysis population (n = 50). OS, overall survival. Shaded areas indicate 95% CI.

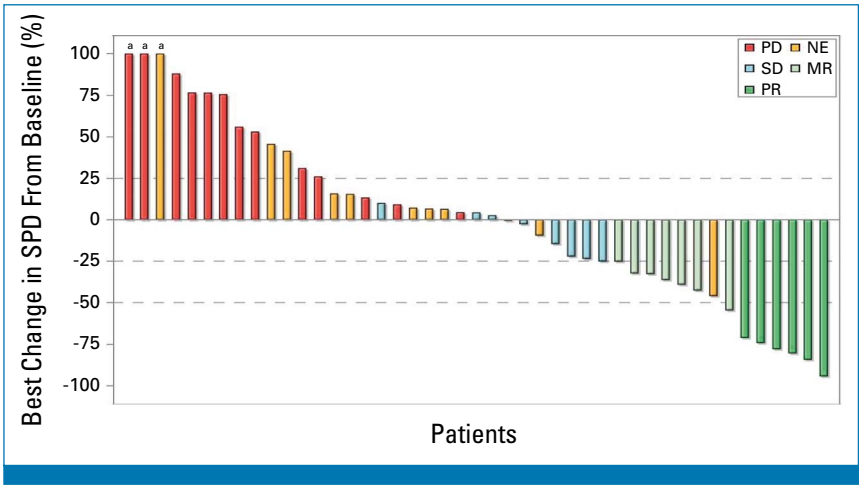

FIG A8. Best percent change in tumor size in the efficacy population (RANO-LGG). Swimmer plot of patients in the efficacy population with measurable target-enhancing lesion by BICR at baseline and postbaseline evaluations. Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored before first on-treatment MR; one patient did not have measurable target lesion. [a]Change >100%. BICR, blinded independent centralized review; MR, minor response; MRI, magnetic resonance imaging; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SPD; sum of products of perpendicular diameters (target nonenhancing lesions per BICR).

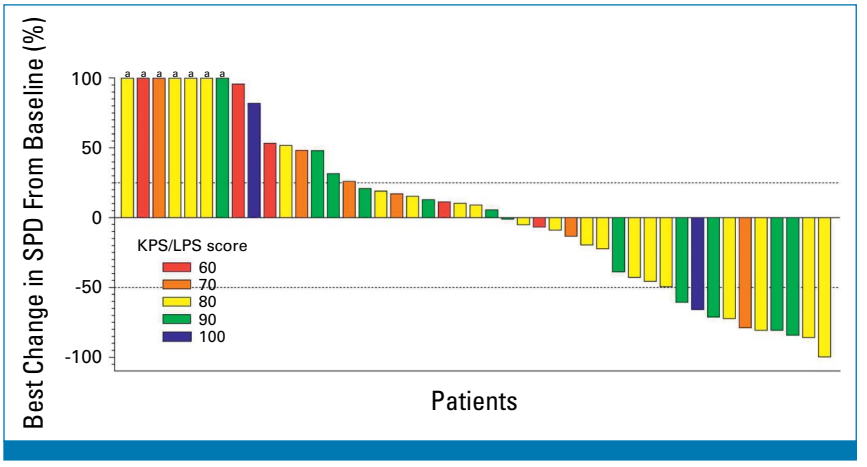

FIG A9. Best percent change in tumor size by baseline performance score. [a]Change >100%. Only patients with measurable target-enhancing lesions at baseline and postbaseline are included (n = 45). KPS, Karnofsky performance score; LPS, Lansky performance score; SPD, sum of products of perpendicular diameters (target-enhancing lesions per blind independent central review).

TABLE A1. ONC201 Studies Contributing Patients to the Efficacy Analysis

Study	Design	Patients	ONC201 Treatment	NCI CTCAE Version	Date of First Patient Treated	Patients Included in Efficacy Analysis (No.)
ONC006 (NCT02525692)[31]	Phase II clinical trial	Age: ≥16 years Recurrent GBM or WHO grade IV glioma, with or without H3 K27M mutation	OL, 625 mg once every week or 625 mg once every 3 weeks	4.0	January 20, 2016	10
ONC013 (NCT03295396)	Phase II clinical trial	Age: ≥18 years Recurrent HGG with H3 K27M mutation	OL, 625 mg once every week	5.0	October 31, 2017	29
ONC014 (NCT03416530)	Phase I clinical trial	Age: 2-18 years Weight: ≥10 kg Recurrent H3 K27M–mutant glioma or newly diagnosed DIPG	OL, 125-625 mg dosed by body weight[a] once every week	5.0	January 30, 2018	2
ONC016	Single-patient compassionate use program	Age: ≥18 years H3 K27M–mutant glioma	OL, 625 mg once every week	4.0	November 2, 2017	1
ONC018 (NCT03134131)[32]	Expanded access program	Age: ≥3 years Weight: ≥10 kg recurrent H3 K27M–mutant glioma, midline HGG, or DIPG	OL, 625 mg once every week for age ≥18 years, dosed by body weight for <18 years	5.0	January 31, 2019	8

Abbreviations: DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma multiforme; H3, histone 3; HGG, high-grade glioma; OL, open-label; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

[a]Allometrically scaled and rounded to 125 mg (the strength of one capsule).

TABLE A2. Eligibility Criteria for Patients Included in the Efficacy Analysis

Inclusion Criterion	Exclusion Criterion
Received at least one dose of ONC201 at 625 mg (or scaled by body weight for patients age <18 years)	DIPG and primary spinal tumors, because of imaging characteristics on gadolinium-enhanced MRI
At least age 2 years	Leptomeningeal spread, cerebrospinal fluid dissemination, atypical and nonastrocytic histologies (eg, ependymoma, ganglioma, and pleomorphic xanthoastrocytoma), or pilocytic astrocytoma and subependymal giant cell astrocytoma
Diffuse glioma with a known H3 K27M mutation confirmed by immunohistochemistry or sequencing	
Tumor in midline brain structure (thalamus, hypothalamus, basal ganglia, brainstem [non-DIPG], cerebellum, cerebellar peduncle, midline cortex, corpus callosum, pineal region, optic tract, or optic chiasm)	
Progressive, measurable disease on contrast-enhanced brain MRI by RANO-HGG criteria	
Previous therapy with at least radiation and an interval of at least 90 days from the completion of radiation to the first dose of ONC201	
Previous therapy with the following, provided that sufficient washout had elapsed: Temozolomide (23 days), Antibodies including bevacizumab (42 days) Other antitumor therapies (28 days)	
KPS/LPS ≥60	
Stable or decreasing corticosteroid dose for at least 3 days before baseline scan	

Abbreviations: DIPG, diffuse intrinsic pontine glioma; H3, histone 3; KPS, Karnofsky performance score; LPS, Lansky performance score; MRI, magnetic resonance imaging; RANO-HGG, response assessment in neuro-oncology high-grade glioma;

TABLE A3. Baseline Characteristics and Response Parameters Among Patients Responding by RANO-HGG, RANO-LGG, or both RANO-HGG and RANO-LGG Criteria

Age, Years	Sex	Race	Body Weight, kg	KPS/ LPS	Tumor Location	Base Enhancing Tumor Size by BICR, cm^2	H3 K27M Detection Method	No. of Recurrences Before ONC201	Previous TMZ	Days Since Recurrence	Days Since Previous RT	Daily Steroid Dose (Dex equivalent), mg	Response by RANO-HGG, LGG, or Both Criteria?	RANO-HGG		RANO-LGG	
														TTR	DOR	TTR	DOR
20	Female	White	76.7	80	Thalamus	10.2	IHC	1	No	19	139	0.5	Both	185	444[a]	185	42
38	Male	White	110	90	Thalamus	13.2	NGS	1	Yes	29	95	4	Both	337	104[a]	59	382
32	Female	White	88	70	Thalamus	9.5	IHC	1	Yes	1	212	0	Both	476	335	533	278[a]
55	Female	White	68.2	90	Cerebellum	3.1	IHC	1	Yes	27	160	6.25	Both	57	222	57	222
54	Male	White	91.2	90	Thalamus	14.0	IHC	1	Yes	7	91	4	Both	337	224[a]	225	336[a]
37	Male	White	95	80	Thalamus	1.6	IHC	2	Yes	27	272	1.3125	Both	83	462	83	462
8	Male	Other	28.8	80	Thalamus	37.0	IHC	1	No	21	234	0	Both	273	113	105	335
51	Male	White	106.6	80	Thalamus	10.5	IHC	1	Yes	15	227	4	Both	223	138	49	312
22	Female	Other	67.1	90	Thalamus	3.7	IHC	1	Yes	14	139	0	HGG	147	924	—	—
51	Male	White	89.4	100	Brainstem (non-DIPG)	5.8	IHC	2	Yes	13	167	0	HGG	476	63[a]	—	—
29	Female	White	63.1	80	Hypothalamus	6.5	IHC	1	Yes	6	103	1.125	LGG	—	—	138	0[a]
42	Female	White	71.7	90	Brainstem (non-DIPG)	2.8	IHC	1	Yes	38	914	0	LGG	—	—	58	108
22	Female	White	69.3	80	Thalamus	10.4	IHC	1	Yes	70	211	0	LGG	—	—	138	188
24	Female	White	102	80	Thalamus	18.0	IHC	2	Yes	45	121	0	LGG	—	—	109	280
29	Female	White	199.1	80	Thalamus	14.4	IHC	2	Yes	23	119	6	LGG	—	—	222	112[a]

Abbreviations: BICR, blinded independent centralized review; Dex, dexamethasone; DIPG, diffuse intrinsic pontine glioma; DOR, duration of response; H3, histone 3; HGG, high-grade glioma; IHC, immunohistochemistry; KPS, Karnofsky performance score; LGG, low-grade glioma; LPS, Lansky performance score; NGS, next-generation sequencing; RANO, Response Assessment in Neuro-Oncology; RT, radiotherapy; TMZ, temozolomide; TTR, time to response.

[a]Censored.

TABLE A4. Corticosteroid and Performance Score Response in the Efficacy Population

Parameter	Efficacy Population
Corticosteroid response	
Evaluable patients, No.	15
Response rate, No. (%) [95% CI]	7 (46.7) [21.3 to 73.4]
TTR, months, median (range)	3.7 (1.9-5.6)
Performance score response	
Evaluable patients, No.	34
Response rate, No. (%) [95% CI]	7 (20.6) [8.7 to 37.9]
TTR, months, median (range)	3.5 (1.9-22.4)

Abbreviations: KPS, Karnofsky performance score; LPS, Lansky performance score; TTR, time to response.
[a]Corticosteroid response: ≥50% reduction in average daily corticosteroid dose compared with baseline with stable or improved KPS/LPS. Must be confirmed at the next analysis timepoint. Corticosteroids were converted into a dexamethasone equivalent dose. Baseline ≥4 mg daily dexamethasone at baseline was evaluable.
[b]Performance score response: increase in KPS/LPS compared with baseline with stable or reduced corticosteroid use. Must be confirmed at the next analysis timepoint. Baseline KPS/LPS ≤80 was evaluable.

TABLE A5. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients

TEAE, No. (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Patients with at least one TEAE	2 (4.0)	12 (24.0)	28 (56.0)	6 (12.0)	1 (2.0)	49 (98.0)
Fatigue	10 (20.0)	6 (12.0)	7 (14.0)	0	0	23 (46.0)
Nausea	12 (24.0)	5 (10.0)	1 (2.0)	0	0	18 (36.0)
Headache	8 (16.0)	4 (8.0)	4 (8.0)	0	0	16 (32.0)
Fall	8 (16.0)	6 (12.0)	0	0	0	14 (28.0)
Vomiting	10 (20.0)	2 (4.0)	1 (2.0)	0	0	13 (26.0)
Gait disturbance	2 (4.0)	7 (14.0)	3 (6.0)	0	0	12 (24.0)
Dizziness	8 (16.0)	2 (4.0)	0	0	0	10 (20.0)
Lymphocyte count decreased	4 (8.0)	4 (8.0)	2 (4.0)	0	0	10 (20.0)
Dysarthria	3 (6.0)	2 (4.0)	4 (8.0)	0	0	9 (18.0)
Confusional state	4 (8.0)	3 (6.0)	1 (2.0)	0	0	8 (16.0)
Dysphagia	3 (6.0)	3 (6.0)	2 (4.0)	0	0	8 (16.0)
Hemiparesis	2 (4.0)	4 (8.0)	2 (4.0)	0	0	8 (16.0)
Paresthesia	8 (16.0)	0	0	0	0	8 (16.0)
Platelet count decreased	7 (14.0)	0	0	0	0	7 (14.0)
ALT increased	4 (8.0)	2 (4.0)	0	0	0	6 (12.0)
AST increased	4 (8.0)	2 (4.0)	0	0	0	6 (12.0)
Dyspnea	3 (6.0)	1 (2.0)	2 (4.0)	0	0	6 (12.0)
Hyperglycemia	5 (10.0)	0	1 (2.0)	0	0	6 (12.0)
Hypokalemia	6 (12.0)	0	0	0	0	6 (12.0)
Muscular weakness	3 (6.0)	3 (6.0)	0	0	0	6 (12.0)
Edema peripheral	4 (8.0)	1 (2.0)	1 (2.0)	0	0	6 (12.0)
Urinary tract infection	0	5 (10.0)	1 (2.0)	0	0	6 (12.0)
Vision blurred	3 (6.0)	3 (6.0)	0	0	0	6 (12.0)
Anemia	4 (8.0)	1 (2.0)	0	0	0	5 (10.0)
Aphasia	0	4 (8.0)	1 (2.0)	0	0	5 (10.0)
Arthralgia	3 (6.0)	1 (2.0)	1 (2.0)	0	0	5 (10.0)
Constipation	5 (10.0)	0	0	0	0	5 (10.0)
Cough	1 (2.0)	3 (6.0)	1 (2.0)	0	0	5 (10.0)
Decreased appetite	1 (2.0)	3 (6.0)	1 (2.0)	0	0	5 (10.0)
Hypertension	0	4 (8.0)	1 (2.0)	0	0	5 (10.0)
Hypoalbuminemia	3 (6.0)	2 (4.0)	0	0	0	5 (10.0)
Insomnia	3 (6.0)	2 (4.0)	0	0	0	5 (10.0)
Urinary incontinence	2 (4.0)	3 (6.0)	0	0	0	5 (10.0)
Weight decreased	0	5 (10.0)	0	0	0	5 (10.0)
Weight increased	2 (4.0)	2 (4.0)	1 (2.0)	0	0	5 (10.0)
Amnesia	3 (6.0)	1 (2.0)	0	0	0	4 (8.0)
Asthenia	0	4 (8.0)	0	0	0	4 (8.0)
Ataxia	0	3 (6.0)	1 (2.0)	0	0	4 (8.0)
Back pain	2 (4.0)	1 (2.0)	1 (2.0)	0	0	4 (8.0)
Blood lactate dehydrogenase increased	4 (8.0)	0	0	0	0	4 (8.0)
Candida infection	0	4 (8.0)	0	0	0	4 (8.0)
Diarrhea	3 (6.0)	1 (2.0)	0	0	0	4 (8.0)
Dysphonia	2 (4.0)	2 (4.0)	0	0	0	4 (8.0)
Encephalopathy	1 (2.0)	0	2 (4.0)	0	1 (2.0)	4 (8.0)
Hydrocephalus	0	0	4 (8.0)	0	0	4 (8.0)
Hypocalcemia	4 (8.0)	0	0	0	0	4 (8.0)
Hypoxia	0	1 (2.0)	2 (4.0)	1 (2.0)	0	4 (8.0)
Memory impairment	3 (6.0)	1 (2.0)	0	0	0	4 (8.0)
Pain in extremity	4 (8.0)	0	0	0	0	4 (8.0)
Pyrexia	4 (8.0)	0	0	0	0	4 (8.0)
Rash maculopapular	2 (4.0)	0	2 (4.0)	0	0	4 (8.0)
Somnolence	3 (6.0)	1 (2.0)	0	0	0	4 (8.0)
Amylase increased	3 (6.0)	0	0	0	0	3 (6.0)

(continued on following page)

TABLE A5. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients (continued)

TEAE, No. (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Aspiration	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Brain edema	0	0	0	3 (6.0)	0	3 (6.0)
Cognitive disorder	3 (6.0)	0	0	0	0	3 (6.0)
Dehydration	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Depressed level of consciousness	0	2 (4.0)	1 (2.0)	0	0	3 (6.0)
Depression	2 (4.0)	1 (2.0)	0	0	0	3 (6.0)
Diplopia	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Dyspepsia	3 (6.0)	0	0	0	0	3 (6.0)
Facial paresis	2 (4.0)	1 (2.0)	0	0	0	3 (6.0)
Hemiparesthesia	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Hypermagnesemia	3 (6.0)	0	0	0	0	3 (6.0)
Hypernatremia	2 (4.0)	0	0	1 (2.0)	0	3 (6.0)
Hyponatremia	3 (6.0)	0	0	0	0	3 (6.0)
Irritability	3 (6.0)	0	0	0	0	3 (6.0)
Nasal congestion	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Nephrolithiasis	1 (2.0)	0	2 (4.0)	0	0	3 (6.0)
Neutrophil count decreased	1 (2.0)	2 (4.0)	0	0	0	3 (6.0)
Oral candidiasis	2 (4.0)	1 (2.0)	0	0	0	3 (6.0)
Oropharyngeal pain	3 (6.0)	0	0	0	0	3 (6.0)
Pulmonary embolism	0	0	3 (6.0)	0	0	3 (6.0)
Upper respiratory tract infection	2 (4.0)	1 (2.0)	0	0	0	3 (6.0)
WBC count decreased	0	3 (6.0)	0	0	0	3 (6.0)

Abbreviation: TEAE, treatment-emergent adverse event.

TABLE A6. SAEs

SAE, No. (%)	All Patients (N = 50)
Patients with at least one SAE	23 (46.0)
Hydrocephalus	4 (8.0)
Nausea	4 (8.0)
Brain edema	3 (6.0)
Encephalopathy	3 (6.0)
Headache	3 (6.0)
Pulmonary embolism	3 (6.0)
Anal incontinence	2 (4.0)
Dyspnea	2 (4.0)
Gait disturbance	2 (4.0)
Seizure	2 (4.0)
Vomiting	2 (4.0)
Acute respiratory distress syndrome	1 (2.0)
Agitation	1 (2.0)
Ataxia	1 (2.0)
Back pain	1 (2.0)
Chest pain	1 (2.0)
Confusional state	1 (2.0)
Deep vein thrombosis	1 (2.0)
Depressed level of consciousness	1 (2.0)
Dysarthria	1 (2.0)
Dysphagia	1 (2.0)
Fall	1 (2.0)
Hemorrhage intracranial	1 (2.0)
Hypernatremia	1 (2.0)
Hypophosphatemia	1 (2.0)
Hypoxia	1 (2.0)
Nephrolithiasis	1 (2.0)
Perirectal abscess	1 (2.0)
Pneumonia	1 (2.0)
Pneumothorax	1 (2.0)
Pulmonary infarction	1 (2.0)
Pulmonary edema	1 (2.0)
Respiratory distress	1 (2.0)
Rib fracture	1 (2.0)
Sepsis	1 (2.0)
Urinary incontinence	1 (2.0)
Urinary retention	1 (2.0)
Urinary tract infection	1 (2.0)

Abbreviation: SAE, serious adverse event.

TABLE A7. TEAEs Leading to Discontinuations, Reductions, and Interruptions

TEAE	All Patients (N = 50), No. (%)
Patients with a TEAE leading to discontinuation, reduction, or interruption	4 (8.0)
Nausea	1 (2.0)
Vomiting	1 (2.0)
Chest pain	1 (2.0)
Gait disturbance	1 (2.0)
Influenza	1 (2.0)
Urinary tract infection	1 (2.0)
Encephalopathy	1 (2.0)
Headache	1 (2.0)
Hydrocephalus	1 (2.0)
Confusional state	1 (2.0)
Dyspnea	1 (2.0)
Pulmonary embolism	1 (2.0)

Abbreviation: TEAE, treatment-emergent adverse event.