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Dordaviprone (ONC201) in a Pediatric Patient With Recurrent H3 K27M-Mutant Diffuse Glioma and Leptomeningeal Disease

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Conclusions

- Therapeutic options for patients with H3 K27M-mutant diffuse glioma and leptomeningeal disease (LMD) remain limited
- The evidence provided in this case report supports a potential therapeutic role for dordaviprone in recurrent H3 K27M-mutant diffuse glioma and LMD
- Given the retrospective, single-patient nature of this report, further evaluation of dordaviprone in this population is warranted to further characterize its clinical activity and safety profile

References:
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Conflicts of Interest:
NEW is an employee of Jazz Pharmaceuticals. GB and DNK have received research funding from Jazz Pharmaceuticals. FDC and TF have no conflicts of interest to declare.

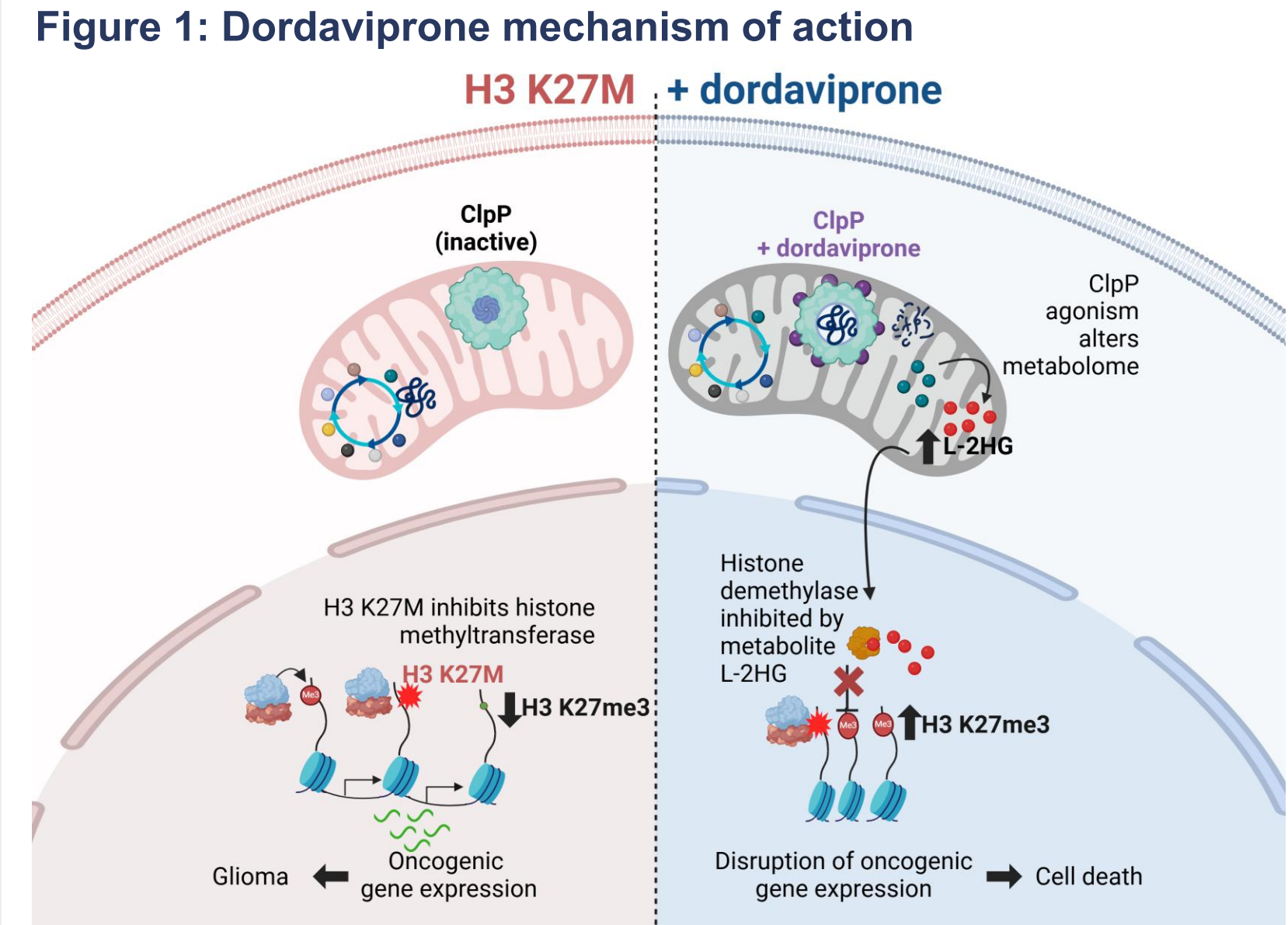


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Introduction

H3 K27M-mutant diffuse glioma

- H3 K27M-mutant diffuse glioma is a molecularly and clinically distinct subtype of CNS WHO Grade 4 glioma with a median overall survival (mOS) of approximately 1 year from diagnosis and 5 months following recurrence¹⁻⁴.
- The central hallmark of H3 K27M-mutant diffuse glioma is the global loss of H3 K27 trimethylation (H3 K27me3), resulting in widespread epigenetic dysregulation and oncogenic gene expression, ultimately driving a highly aggressive tumor phenotype (Figure 1)⁵.
- Treatment options for H3 K27M-mutant diffuse glioma are limited:
 - Surgical resection is difficult due to tumor location and does not confer a survival benefit over biopsy alone⁷.
 - Frontline treatment consists of radiation therapy (RT) with or without chemotherapy⁸.
 - Until recently, there were no approved systemic therapies specifically for H3 K27M-mutant diffuse glioma⁹.
- The occurrence of LMD in H3 K27M-mutant diffuse midline glioma (DMG) has been reported in 3 retrospective analyses⁹⁻¹¹.



H3 K27M-mutant diffuse glioma is defined by a global reduction in H3 K27me3 levels. Dordaviprone is an agonist of the mitochondrial caseinolytic protease P (ClpP), which impairs mitochondrial metabolism in H3 K27M-mutant diffuse glioma cells. ClpP agonism reduces the expression of oxoglutarate dehydrogenase (OGDH), a regulator of alpha-ketoglutarate (α-KG). This metabolic shift leads to the accumulation of α-KG, which is subsequently converted into L-2-hydroxyglutarate (L-2HG), a metabolite that negatively regulates histone demethylases, resulting in increased H3 K27me3 levels, and subsequent cellular stress, impaired growth, and apoptosis.

Dordaviprone (ONC201)

- Dordaviprone is a first-in-class, oral, CNS-penetrant small-molecule imipridone that acts as a mitochondrial caseinolytic protease P (ClpP) agonist and dopamine receptor DR (DRD2) antagonist.¹²⁻¹³ It is the first FDA-approved systemic treatment specifically for H3 K27M-mutant DMG that has progressed following prior therapy¹⁴.
- Altered mitochondrial metabolism induced by dordaviprone (ClpP activation) reverses H3 K27 trimethyl (H3 K27me3)-loss, the central hallmark of H3 K27M-mutant DMG, resulting in cellular stress, impaired growth, and apoptosis (Figure 1)¹⁵.
- Key efficacy and safety results of dordaviprone:
 - Efficacy (N = 50, recurrent H3 K27M-mutant DMG):** 28.0% ORR (95% CI, 16-42), 4.6 mo mTTR (range, 1.6-15.9), and 10.4 mo mDOR (95% CI, 7.4-15.4) by BICR-confirmed RANO 2.0. The mOS from first dose was 13.7 mo (95% CI, 8.0-20.3)¹⁶⁻¹⁷.
 - Safety (N = 376, recurrent glioma):** The most common adverse events (AEs) in the pooled safety population (all grades, grades 3 or 4) were fatigue (34%, 3.2%), headache (32%, 4.3%), vomiting (24%, 2.7%), nausea (24%, 0.8%), and musculoskeletal pain (20%, 2.9%). Permanent discontinuation of dordaviprone due to an adverse reaction occurred in 2.1% of patients¹⁴.
- Patients with LMD were excluded from prior dordaviprone response analyses due to challenges with radiographic evaluation by standard response criteria¹⁸.

Methods

ONC028 (NCT04617002) was a US-based expanded access protocol to provide dordaviprone access to patients ineligible for clinical trials, including patients with LMD

- Treatment:** Eligible patients were treated with 625 mg dordaviprone once weekly or dose equivalent based on body weight for pediatric patients weighing less than 52.5 kg
- Assessments:** MRI every 2 months for 1 year and every 2-3 months thereafter. AEs were assessed by National Cancer Institute (NCI) Common Terminology Criteria for AEs version 5.0 (CTCAE v5.0) criteria
- Duration of Therapy:** Treatment continued until unacceptable AEs, withdrawal of consent, or disease progression (treatment was permitted to continue post-progression at the discretion of the treating physician)
- Key Eligibility Criteria are described in Table 1

Table 1: Key eligibility criteria (ONC028)	
Key Eligibility Criteria ^a	
Ineligible for an ongoing dordaviprone trial	
Confirmed H3 K27M-mutant glioma (except DIPG):	
• DIPG:	
• May have confirmed H3 K27M mutation or tissue unavailable for confirmation	
• H3 K27-wt are ineligible	
• Confirmation of progression not required	
• Recurrent/progressive spinal tumor with documented H3 K27M mutation	
• Recurrent DMG with H3 K27M mutation and radiographic evidence of leptomeningeal spread ^b	
Body weight ≥10 kg	
Prior RT	
Bevacizumab use for RT necrosis or symptom management was permitted	

^aFull inclusion and exclusion criteria are described within ClinicalTrials.gov (NCT04617002). ^bApplies to reported patient. DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; RT, radiation therapy; wt, wild type.

Patient case

Patient diagnostic profile and medical history

- Following a diagnostic MRI and stereotactic biopsy, an 11-year-old female patient weighing 43 kg was diagnosed with progressive right thalamic H3 K27M-mutant DMG and extensive LMD on January 26, 2023 (Figure 2, Table 2)
- At diagnosis, the patient had a 1-month history of headaches, as well as a history of seizure, nausea, difficulty eating, voiding and stooling, irritability, left hemiparesis, and somnolence, and had a Lansky Performance Status (LPS) of 80. The patient did not have any pre-existing medical conditions prior to her cancer diagnosis
- First-line radiation therapy (RT) and temozolomide were initiated on February 7, 2023; additional treatment with dabrafenib plus trametinib was initiated in early May 2023 and a single dose of bevacizumab was given on July 7, 2023 (Figure 2)
 - Tumor progression in the right thalamic region was documented on May 10, 2023 (Figure 3)
- Radiographic progression was accompanied by a LPS of 50 and dexamethasone treatment of 2 mg/day. Clinical deterioration included need for assisted ambulation, gastrostomy tube dependence, and worsened fatigue/somnolence

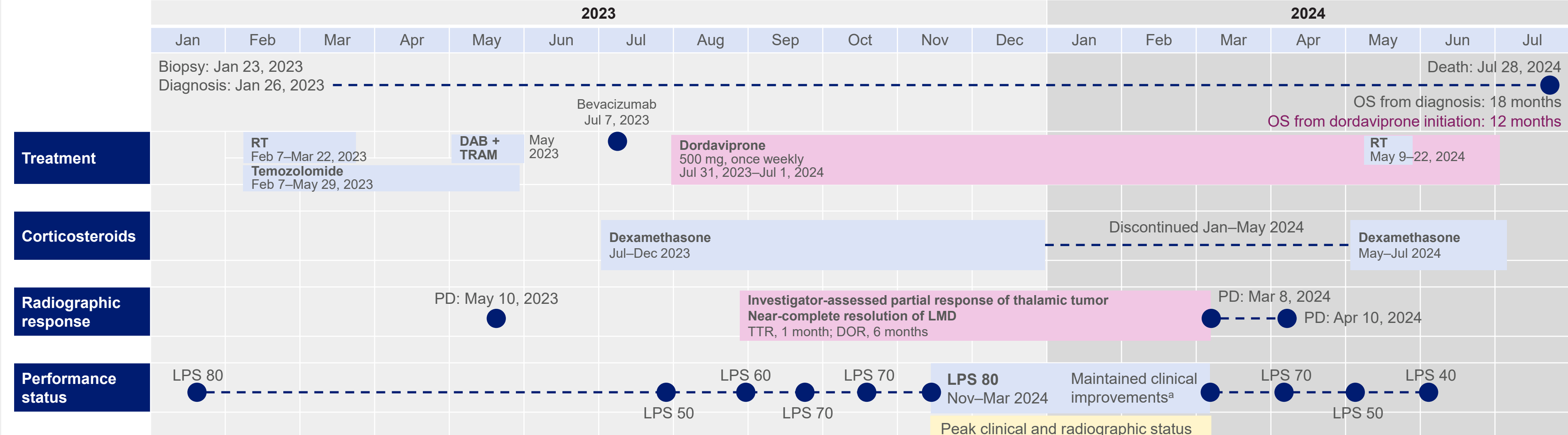
Results

Table 2: Patient profile, past medical history, and diagnosis

Characteristic	
Diagnosis	Diffuse midline glioma, H3 K27-altered, H3 K27M-mutant subtype (CNS WHO Grade 4) Thalamic: Approximately 4.5 × 3.5 cm in right thalamus with posterior dissemination into left thalamus LMD: Affected the brainstem and diencephalon surfaces, with cisternal involvement (quadrigeminal, ambient, perimesencephalic, interpeduncular). Marked enhancement and thickening along the optic chiasm and cranial nerves II, III, V, VII, and VIII, with extension into Meckel's caves and cavernous sinuses were observed. Additional enhancement was seen along cortical sulci and cerebellar folia
Tumor Locations	
Immunohistochemical Profile	Positivity for GFAP, OLIG2, Ki67 (40% of tumor cells), P53 (mutated pattern), ATRX (preserved expression), INI-1, and H3 K27M accompanied with loss of H3 K27me3. IDH1 R132H was negative.
Molecular Alterations (NGS)	- H3-3A (K27M), <i>PTPN11</i> (N308S), and <i>TP53</i> (L252P) - Tumor mutational burden was 0 mut/Mb, and microsatellite instability was stable (3% of unstable sites)
Treatment History Prior to ONC028	Levetiracetam: administered for seizure at presentation Radiation therapy: 36 Gy dose to the craniospinal axis, 54 Gy in 30 fractions at 1.8 Gy to the right thalamic lesion (February 7, 2023, to March 22, 2023) Temozolomide: 5 cycles (February 7, 2023, to May 29, 2023) Dabrafenib and trametinib: Off-label, unknown dose and duration (May 2023) Bevacizumab: Single dose July 7, 2023

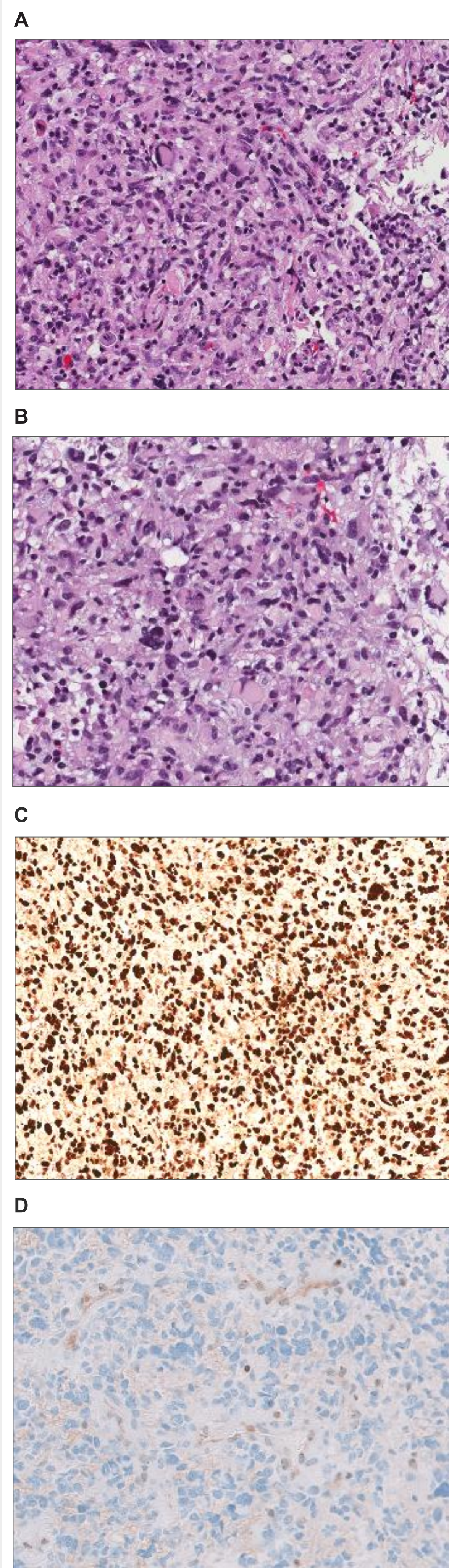
CNS, central nervous system; DMG, diffuse midline glioma; LMD, leptomeningeal disease; NGS, next-generation sequencing; WHO, World Health Organization.

Figure 2: Patient treatment journey



^aNeurologic status improved from assisted ambulation, gastrostomy tube dependence, and fatigue/somnolence to unassisted ambulation, expressive speech, and resolution of focal neurologic deficits. DAB, dabrafenib; DOR, duration of response; LPS, Lansky Performance Status; LMD, leptomeningeal disease; OS, overall survival; PD, progressive disease; RT, radiation therapy; TRAM, trametinib; TTR, time-to-response.

Figure 3: Histopathologic and immunohistochemical features of the thalamic lesion

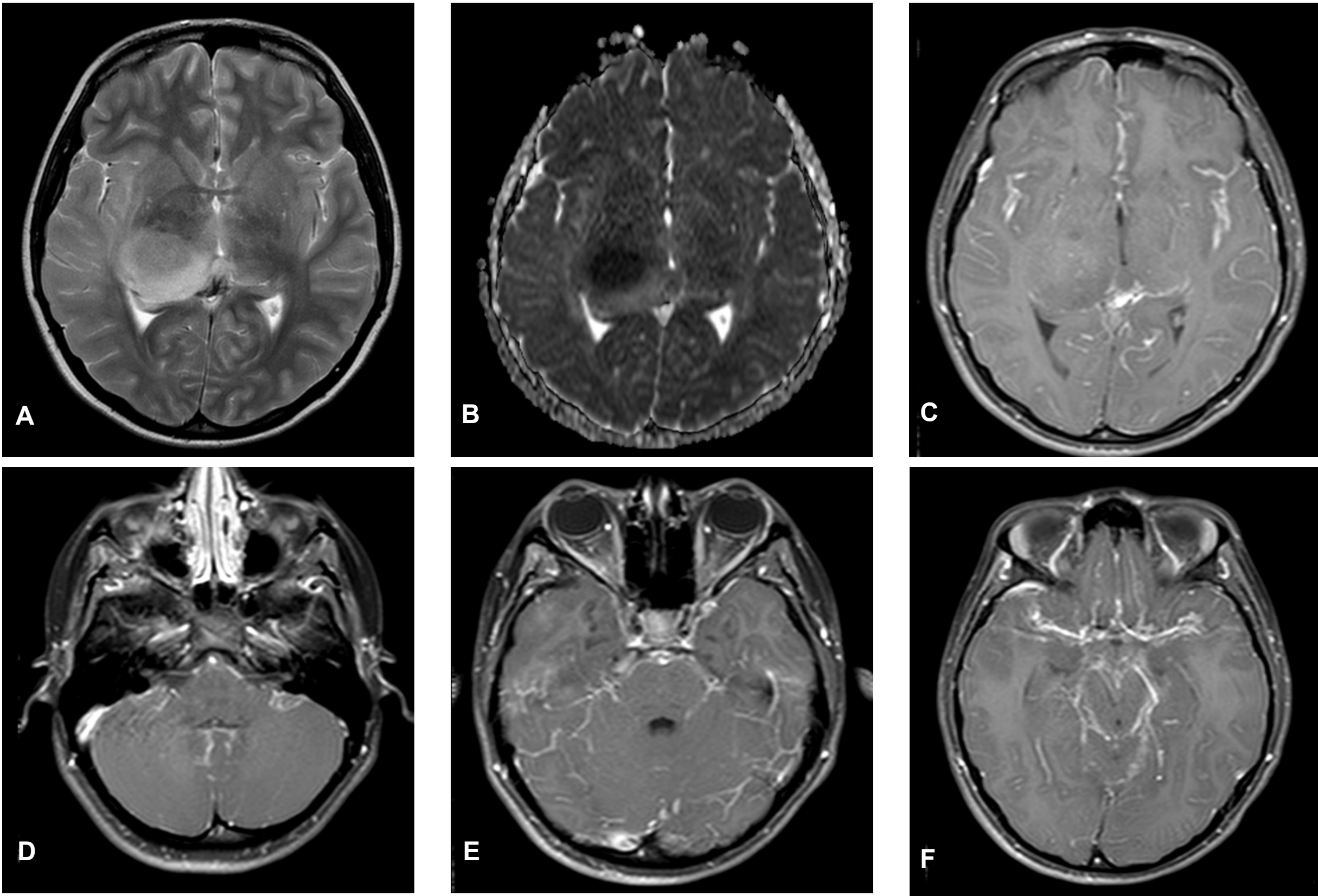


The tumor showed high cellularity, composed by pleomorphic astrocytic cells, displaying enlarged and hyperchromatic nuclei (A and B). By immunohistochemistry, there was diffuse nuclear positivity for H3 K27M antibody (C), with loss of H3 K27me3 (D). These findings were consistent with the diagnosis of diffuse midline glioma, H3 K27-altered, H3 K27M-mutant subtype (CNS WHO grade 4).

Dordaviprone treatment

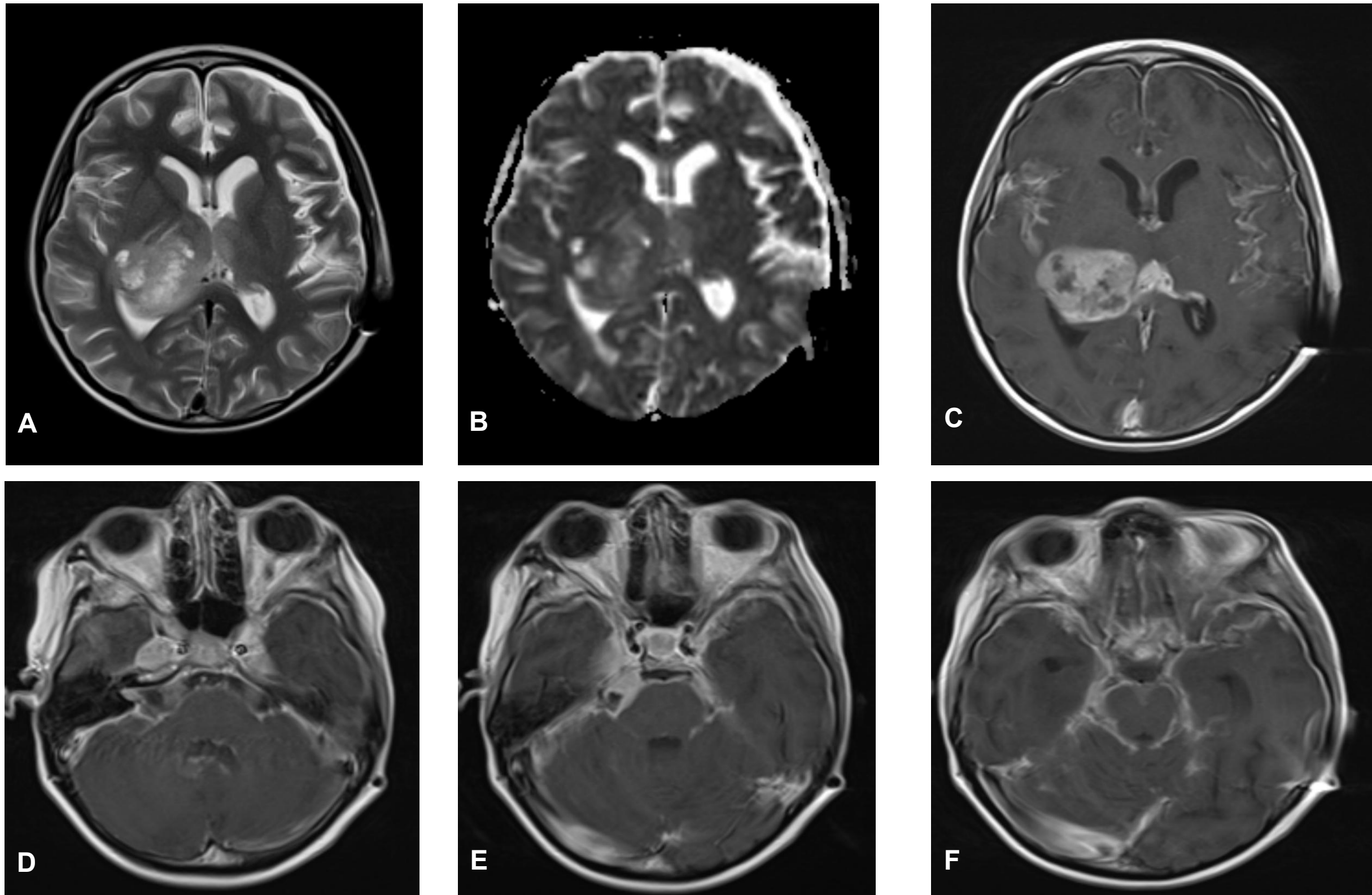
- Dordaviprone was initiated at 500 mg once weekly on July 31, 2023, and continued for 11 months
- Safety:** Grade 2 fatigue on the day after first dordaviprone dose, and episodic vomiting occurred twice over the course of therapy. No additional adverse events were reported
- Radiographic Response:** One month after dordaviprone initiation, the patient achieved an investigator-assessed radiographic partial response of the thalamic tumor and near-complete resolution of LMD, both sustained for 6 months (BOR of 67% per RAPNO criteria; Figures 2 and 6)
- Clinical Benefits:** LPS improved from 50 to 80 (after 3 months of dordaviprone treatment) and was maintained for 4 months. Dexamethasone was tapered from 2 mg/day to discontinuation. Neurologic status improved from assisted ambulation, gastrostomy tube dependence, and fatigue/somnolence to unassisted ambulation, expressive speech, and resolution of focal neurologic deficits. Due to clinical improvement, the patient resumed normal activities (eg, attending school independently and swimming)
- Treatment with dordaviprone was continued beyond progression, with a total therapy duration of 11 months. OS was 12 months from dordaviprone initiation and 18 months from diagnosis**

Figure 4: Diagnostic MRIs (January 23, 2023)



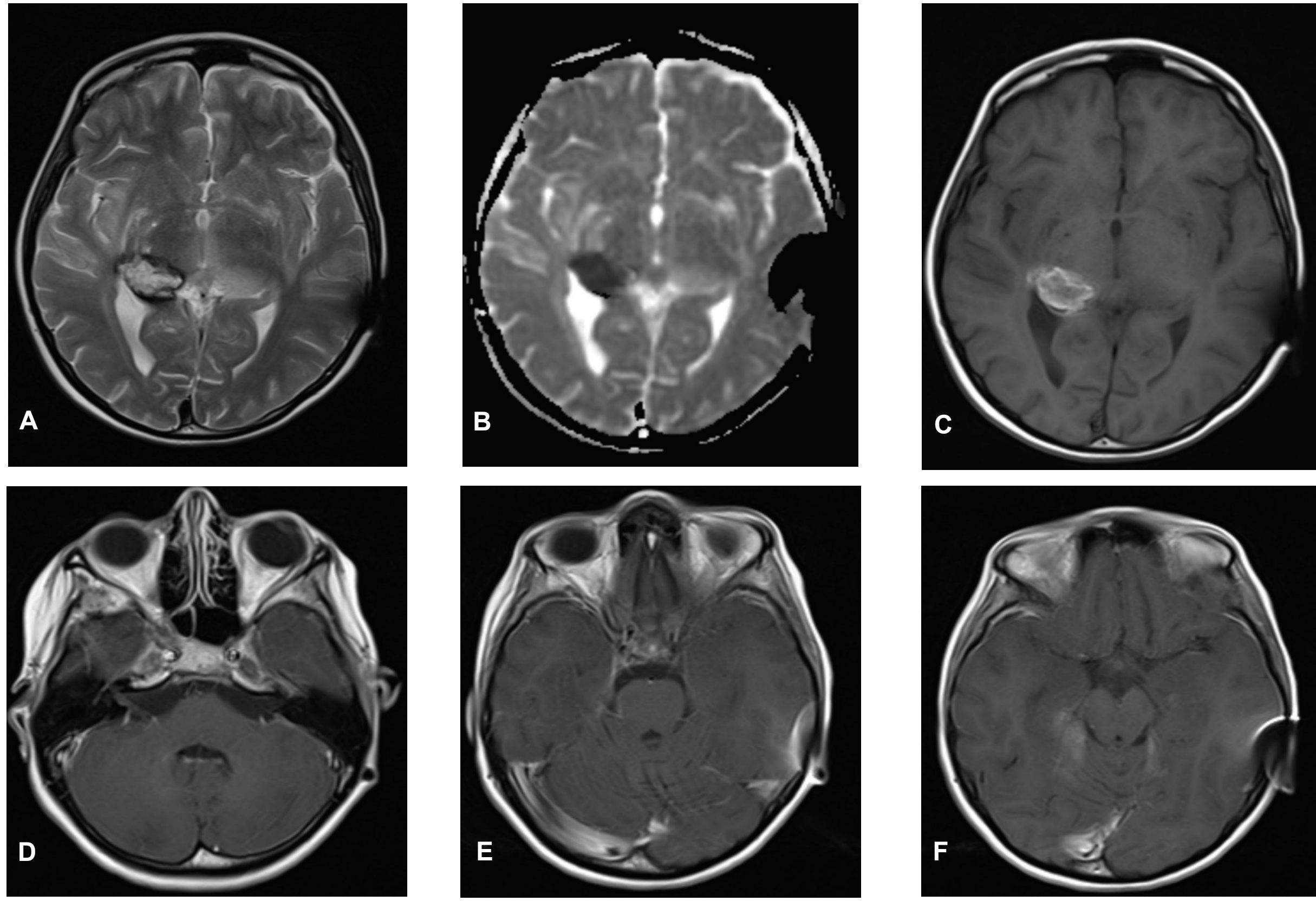
T2-weighted image reveals a heterogeneous hyperintense nodular infiltrative lesion in the right thalamus (A). ADC map shows areas of restricted diffusion within the lesion (B). Postcontrast axial T1 image shows no significant gadolinium enhancement of the lesion. Findings suggest leptomeningeal dissemination, with abnormal contrast enhancement along the optic sulci and Sylvian fissures (C). Postcontrast axial T1 images reveal leptomeningeal dissemination, with abnormal gadolinium enhancement along the basal cisterns, cortical sulci, and some cranial nerves (D-F).

Figure 5: Two-month post-RT MRIs, prior to dordaviprone administration (May 10, 2023)



T2-weighted image reveals a heterogeneous hyperintense nodular infiltrative lesion in the right thalamus (A). ADC map shows areas of restricted diffusion within the lesion (B). Postcontrast axial T1 image shows no significant gadolinium enhancement of the lesion. Findings suggest leptomeningeal dissemination, with abnormal contrast enhancement along the optic sulci and Sylvian fissures (C). Postcontrast axial T1 images reveal leptomeningeal dissemination, with abnormal gadolinium enhancement along the basal cisterns, cortical sulci, and some cranial nerves (D-F).

Figure 6: Best response MRIs (December 21, 2023; 5 months after dordaviprone initiation)



T2-weighted image reveals significant decrease in the volume of the right thalamic lesion. Appearance of a new lesion component in the left thalamus (A). ADC map shows a homogeneous restricted diffusion pattern in the right thalamus lesion (B). Non-contrast axial T1 image demonstrates reduced volume of the lesion, with resolution of the contrast uptake, the lesion is spontaneous hyperintense on T1 precontrast image. There was a significant reduction in leptomeningeal enhancement, and there was no contrast uptake in the left thalamic lesion (not shown) (C). Postcontrast axial T1 images reveal a significant reduction in leptomeningeal enhancement (D-F).