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Point/Counterpoint: Dordaviprone for diffuse midline glioma - A landmark approval or a premature step?

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Abstract

Diffuse midline glioma (DMG) remains one of the most aggressive and uniformly fatal brain tumors, with a median overall survival (OS) of only 11 months and no systemic therapy yet demonstrating a meaningful survival benefit. Primarily affecting children and young adults, DMG represents an area of profound unmet clinical need where families and oncologists have faced decades of therapeutic stagnation. The recent accelerated approval by the United States (US) Food and Drug Administration (FDA) of dordaviprone (ONC201, Modeyso™) for patients with progressive H3 K27M–altered DMG marks the first regulatory recognition of a systemic therapy for this devastating disease.

The decision has generated both optimism and debate within the neuro-oncology community. For many, the approval symbolizes long-overdue progress and affirms that systemic agents can demonstrate activity in DMG. For others, it raises concerns over whether the current evidence base is sufficient to justify widespread clinical adoption. The accelerated approval pathways allow for earlier access to therapy for serious life-threatening conditions based on surrogate endpoints, such as durable objective response rates (ORRs), while mandating post-approval studies to confirm benefit. However, while approvals using data from single-arm trials can make promising therapies available to patients expeditiously, such exceptional approvals present challenges that must be carefully considered. In the case of dordaviprone, this mechanism was applied following an integrated analysis of early-phase studies (ONC006 (NCT02525692), ONC013 (NCT03295396), ONC014 (NCT03416530),[1] ONC016 (NCT05392374), and ONC018 (NCT03134131))[2] that demonstrated measurable radiographic and biological responses in a subset of patients.

Here, we examine the scientific, clinical, and regulatory context of the dordaviprone approval through contrasting perspectives. We consider both the landmark nature of this decision and the potential risks of overinterpreting preliminary evidence, aiming to clarify what this approval means for current practice and for the future development of therapies in DMG and other brain tumors.

Point: A Landmark Step Forward

Before the approval of dordaviprone for patients with progressive H3 K27M–altered DMG, no pharmacologic intervention had demonstrated a meaningful clinical benefit for DMG, leaving families and clinicians confronting the same devastating prognosis for decades and underscoring the urgent need for therapeutic progress. For many, this approval is not only a scientific milestone but also delivers an urgently needed new therapy to patients and families confronting this uniformly lethal disease with few options.

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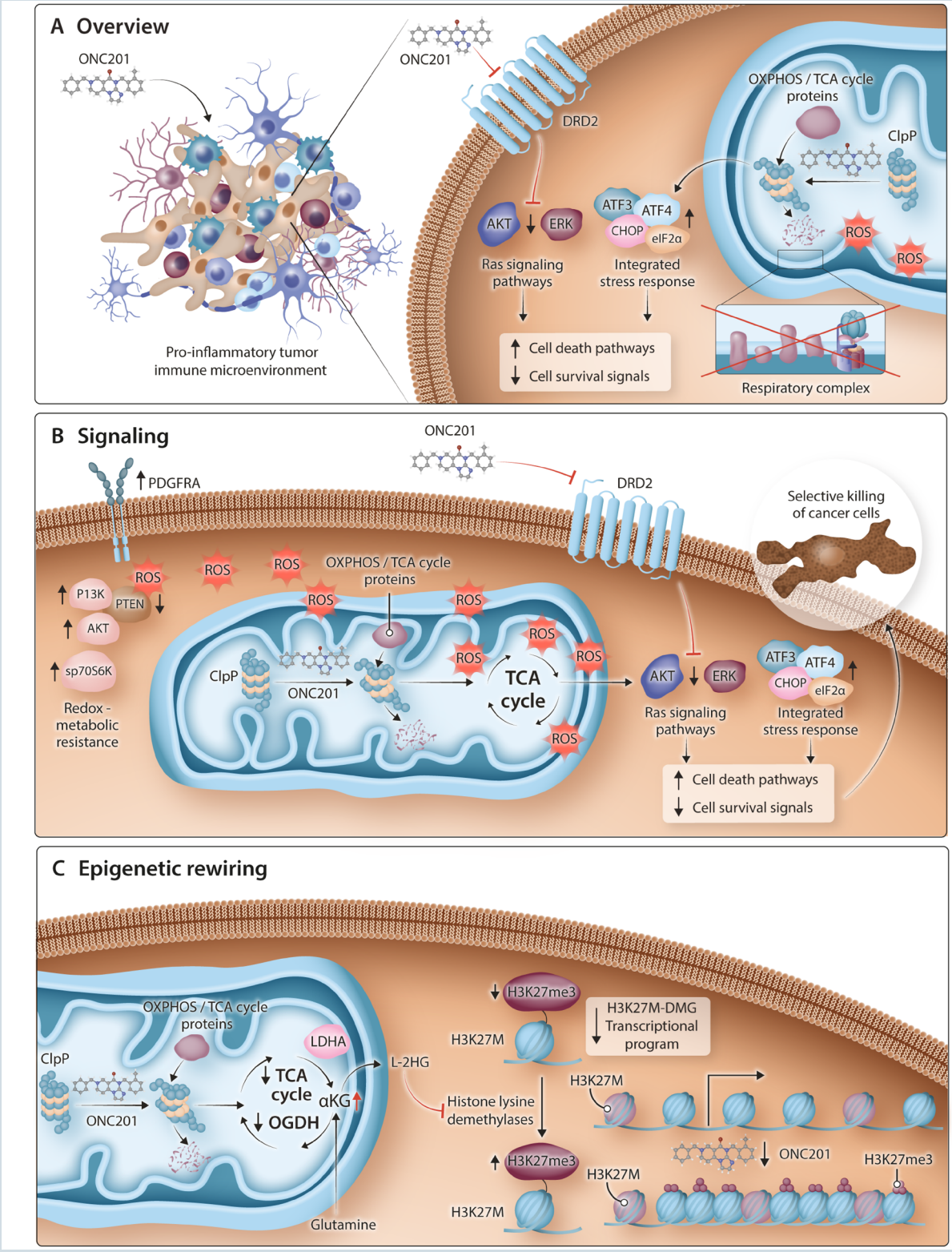

Figure 1. Schematic illustrating the proposed mechanisms of action of dordaviprone (ONC201, Modeyso™) in diffuse midline glioma. Panel A shows dordaviprone acting as a DRD2 antagonist and ClpP agonist, activating the integrated stress response and promoting a pro-inflammatory tumor immune microenvironment. Panel B depicts downstream effects including ERK suppression, mitochondrial dysfunction, activation of the ATF4-CHOP stress pathway, and potential redox-associated resistance mechanisms. Panel C illustrates dordavirpone-induced metabolic and epigenetic reprogramming, including restoration of H3K27me3, altered chromatin accessibility, and transcriptional changes associated with DMG-selective vulnerabilities. Cartoon developed in collaboration with https://www.somersault1824.com/.

From a biological standpoint, dordaviprone offers a mechanistically novel approach. Studies in non-DMG tissues using Bayesian machine learning identified dordaviprone to bind to dopamine receptors, specifically dopamine receptor D2 (DRD2) (Figure 1A).[3] In silico modeling corroborated these studies showing dordaviprone to tightly bind the active site of DRD2.[4] Functionally, in non-central nervous system (CNS) tumors, dordaviprone inhibits cyclic adenosine monophosphate production,[5] to promote tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) independent of functional p53, leading to inhibition of the MAPK/ERK and PI3K/Akt signaling cascades (Figure 1B).[6]

In CNS cancers, DRD2 has been reported to be highly expressed, promoting tumor growth and has emerged as a therapeutic target for gliomas (Figure 1B). H3K27M-mutant DMG and diffuse intrinsic pontine glioma (DIPG) show elevated DRD2 expression, particularly within oligodendrocyte precursor cell–like tumor cell populations, providing a mechanistic rationale for dordaviprone's selective DRD2 antagonism.[7] However, mRNA expression of DRD2 does not correlate with dordaviprone sensitivity in DMG cell lines, nor does molecular inhibition of DRD2 expression modulate dordaviprone response in DMG models,[8] suggesting alternative mechanisms.

The Mechanistic Promise in DMG and DIPG

Dordaviprone exerts antitumor activity in DMG through convergent mitochondrial and epigenetic mechanisms. Its primary target is the ATP-dependent caseinolytic protease proteolytic subunit (ClpP), a mitochondrial serine protease that maintains energy homeostasis by degrading damaged respiratory chain components.[4,8–10] In DMG, ClpP is markedly overexpressed at both the mRNA and protein levels, reflecting the high energy demands of these highly proliferative tumors.[8,9,11] Dordaviprone acts as a potent agonist of ClpP, binding the protease, widening its axial pores, and preventing interaction with its substrate-recognizing chaperone, caseinolytic protease X, leading to non-selective proteolysis of respiratory chain proteins and collapse of mitochondrial function.[9,12] This uncontrolled degradation induces oxidative stress, metabolic crisis, and apoptotic cell death.[9] The centrality of ClpP to dordaviprone's activity has been validated in CRISPR/Cas9 knockout studies,[8,13] where ClpP depletion abolished drug sensitivity in previously responsive DMG cell lines.[8]

Metabolic Reprogramming

At the metabolic level, ClpP activation induces uncontrolled degradation of mitochondrial respiratory chain components, leading to oxidative stress, disruption of tricarboxylic acid (TCA) cycle flux, and altered metabolite ratios such as succinate:α-ketoglutarate (α-KG) (Figure 1C). These mitochondrial perturbations drive a metabolic crisis and apoptotic cell death in DMG cells.[4,8,14] Proteomic profiling of DMG models demonstrates loss of succinate dehydrogenase subunits A (SDHA) and B (SDHB), consistent with electron-transport chain (ETC) complex II degradation and diversion of carbon through glutaminolysis.[8,14] Metabolic tracing and clinical correlates show that dordaviprone suppresses TCA activity while enhancing glutamine metabolism, increasing α-KG levels that are subsequently reduced to L-2-hydroxyglutarate (L-2HG) (Figure 1B).[15] L-2HG is a stereospecific, competitive inhibitor of α-KG–dependent Jumonji lysine demethylases. Knockdown of ClpP or lactate dehydrogenase A, or overexpression of L-2HG dehydrogenase (L-2HGDH), abrogates the restoration of H3K27me3, the degradation of the mitochondrial respiratory chain and its downstream effects on oxidative stress, metabolic dysfunction, and cell death.[15]

Epigenetic Consequences

This metabolism-driven accumulation of L-2HG provides a mechanistic link between mitochondrial stress and epigenetic rewiring (Figure 1C). By transiently inhibiting α-KG–dependent histone demethylases such as KDM6A/B, dordaviprone promotes re-establishment of histone H3 lysine-27 trimethylation (H3K27me3) to wild-type H3 and some restoration of chromatin repression (Figure 1C).[15] Loss of H3K27me3 is a defining molecular feature of all H3K27M-mutant DMGs, and its partial restoration following dordaviprone exposure supports a disease-selective corrective mechanism. In autopsy samples from dordaviprone-treated patients, H3K27M tumor cells displayed increased H3K27me3 by immunohistochemistry compared with untreated DMG patients, across multiple independent cohorts.[15] Chromatin immunoprecipitation sequencing showed higher genome-wide H3K27me3 levels, with enrichment in genes involved in morphogenesis and neuronal differentiation, and redistribution of H3K27me3 from intergenic to genic regions, distinct from the patterns observed in isocitrate dehydrogenase (IDH)-mutant gliomas.[15]

Preclinical and Clinical Correlates

Preclinically and clinically, dordaviprone efficiently crosses the blood-brain barrier, achieves therapeutic CNS concentrations, and prolongs survival in DMG models, demonstrating clear pharmacodynamic engagement.[8,15,16] However, single-agent activity remains modest in patient-derived xenograft mouse models,[4,8,10] indicating that epigenetic reset alone is insufficient for durable control. Incomplete understanding of the systemic consequences of ClpP activation and DRD2 antagonism, spanning metabolic, neuroendocrine, and immune axes, likely explains heterogeneity in patient responses.[9,11] Nonetheless, the convergence of mitochondrial collapse, metabolic rewiring, and epigenetic restoration has provided a compelling rationale for clinical evaluation.

Clinical Evidence

The clinical development of dordaviprone began in recurrent glioblastoma, where an exceptional responder harboring an H3K27M mutation prompted a strategic shift toward DMG.[17] This observation catalyzed the reorientation of subsequent trials toward H3K27M-altered tumors, reflecting both biological rationale and early clinical promise (Figure 2).

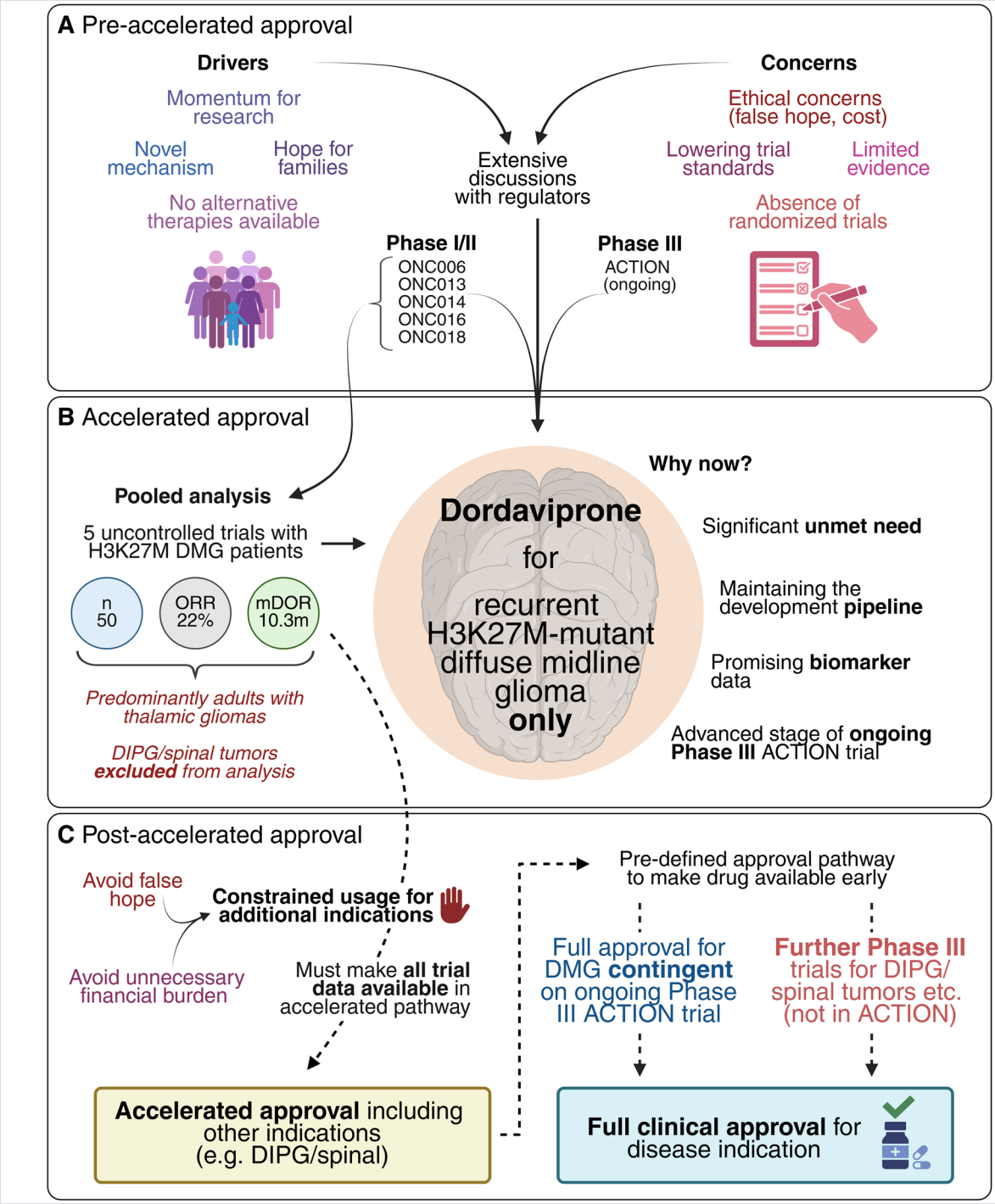

Figure 2. Schematic summarizing the regulatory pathway and rationale for accelerated approval of dordaviprone in H3K27M-mutant diffuse midline glioma. Panel A outlines early-phase clinical trials and regulatory considerations, highlighting unmet clinical need, novel mechanism of action, and concerns regarding limited and non-randomized evidence. Panel B summarizes the integrated analysis supporting accelerated approval, including response rates and duration of response primarily observed in adults with thalamic gliomas, while noting exclusion of DIPG and spinal tumors due to imaging assessment challenges. Panel C depicts the post-approval framework, emphasizing restriction to the approved indication pending confirmation in the phase 3 ACTION trial and the need for additional studies in DIPG and spinal DMG.

Across early-phase and expanded-access studies, radiographic tumor regressions and prolonged survival were observed in a subset of patients with H3K27M-mutant DMG, in particular those with non-pontine or spinal disease.[4,14, 18–20] These signals of activity, although not universal, and in some cases retrospectively analyzed, provided the first evidence of the potential that a systemic therapeutic agent can provide efficacy in this disease context. Notably, dordaviprone became the first compound shown to partially restore H3K27me3 marks *in vivo*,[14] providing a biological correlate of epigenetic reprogramming in treated tumors.

Emerging translational data further support these findings. In responders, tumor-derived DNA in CSF declined over time,[21] suggesting on-treatment molecular response, with metabolomic profiling of CSF demonstrating shifts consistent with ClpP-mediated mitochondrial disruption and altered glutamine/TCA metabolism.[14]Together, these correlative data may suggest target engagement associated with measurable clinical and biochemical changes within the CNS and may support the mechanistic plausibility of the observed responses.

From a safety standpoint, dordaviprone has exhibited a favorable tolerability profile, with predominantly mild gastrointestinal symptoms, fatigue, and transient laboratory abnormalities.[14,20] The absence of severe hematologic or neurologic toxicities distinguishes it from cytotoxic or epigenetic agents previously tested in this population, shifting the risk-benefit calculus toward accessibility and chronic administration, particularly in children and young adults.

Accelerated approval for dordaviprone was granted by the FDA based on durable radiographic responses in patients with recurrent H3 K27M-mutant DMG with measurable disease and ≥90 days from radiation therapy. The median time to response was 8.3 months (95% confidence interval [CI]: 1.9-15.9 months) and duration of response was 11.2 months (95% CI: 3.8-NR).[20] Patients who responded had progression-free survival (PFS) of 19.5 months.

However, this approval was contingent on confirmatory evidence from the ongoing ACTION trial (NCT05580562), a global, randomized, double-blind, placebo-controlled, parallel-group, trial of dordaviprone 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 (625mg) or twice-weekly dordaviprone (625 mg) on two consecutive days.[22] Primary efficacy endpoints are OS and PFS. Importantly, DIPG and spinal cord DMGs are excluded. This trial stopped enrolling at US sites because the drug has become available and it would be challenging to have patients on the non-dordaviprone arm. However, the trial remains open in all non-US sites with continued accrual. Its results will be pivotal in validating clinical benefit in non-pontine, non-spinal DMG and determining whether dordaviprone transitions from accelerated to full approval.

The current efficacy data derive predominantly from adult and adolescent patients with thalamic DMG, rather than pontine or spinal cord tumors. Extrapolating these outcomes to DIPG, a biologically and anatomically distinct subset remains speculative. Early reports in DIPG suggest disease stabilization but without consistent radiographic or molecular confirmation across cohorts.[14] Venneti et al. performed an exploratory retrospective analysis of clinical outcomes of dordaviprone in patients with H3K27M-mutant DMG from two completed trials, ONC201-014 and ONC201-018, which included brainstem (n=41) and thalamic (n=30) H3K27M-DMG patients in the recurrent (n=36), and non-recurrent (n=35) setting. In this analysis, dordaviprone treatment in non-recurrent patients demonstrated a potential survival benefit, compared to an aggregated historical control dataset.[14] Patients with newly diagnosed brainstem tumors treated with dordaviprone showed longer PFS and OS than seen in recently completed brainstem H3K27M-DMG precision medicine study PNOC003.[23] Comparisons with re-irradiation were not performed, despite this now being recognized as a key determinant of improved neurological function[24] and retrospective analyses demonstrating survival benefits in recurrent DMG.[25,26] The absence of such analyses limits interpretation of dordaviprone's contribution to outcome improvements, particularly as many patients in contemporary cohorts receive re-irradiation at progression. We also note that expanding off-label usage of dordaviprone (particularly for newly diagnosed DMG patients post radiotherapy) may further complicate the ability of investigators to undertake comprehensive studies in the DIPG population.

While approximately 374 patients have received dordaviprone across clinical trials and expanded access programs, published data cover only about 43% of this total. Comprehensive, intent-to-treat analyses, including negative and non-durable outcomes, will be essential for a transparent assessment of efficacy, durability, and generalizability, and the results for the remaining 57% of patients enrolled on previous studies should be made available to the scientific community for review. The ACTION trial results are highly anticipated as blinded, placebo-controlled study data, but the trial notably excludes DIPG and spinal DMGs.[22] The next phase of investigation must therefore pair rigorous clinical trial design encompassing all relevant patient populations with complete data disclosure to ensure that enthusiasm remains anchored in evidence (Figure 3).

Regulatory and Ethical Perspective

The accelerated approval of dordaviprone represents a key milestone for DMG. The decision reflects the intent of the accelerated pathway to provide earlier access to potentially beneficial therapies based on surrogate endpoints reasonably likely to predict clinical benefit. In this case, response rate and duration of response were judged adequate surrogates in light of the poor prognosis and limited treatment options. Yet, while DMG is a devastating disease, it is not so uncommon that rigorously designed, well-conducted studies cannot be completed. Continued reliance on small, uncontrolled datasets risks normalizing exceptions rather than establishing standards.

This approval marks the first use of RANO 2.0 criteria, which evaluates both enhancing and non-enhancing disease (which is frequent in DMG, specifically DIPG and thalamic DMG),[27] as the formal standard for response assessment in a regulatory decision for glioma, establishing a precedent for future neuro-oncology drug evaluations (Figure 3).[28]The reliance on standardized, centrally reviewed imaging criteria enhances transparency and reproducibility, setting a framework for subsequent trials in DMG and other diffuse gliomas. The decision also indicates that rare, rapidly

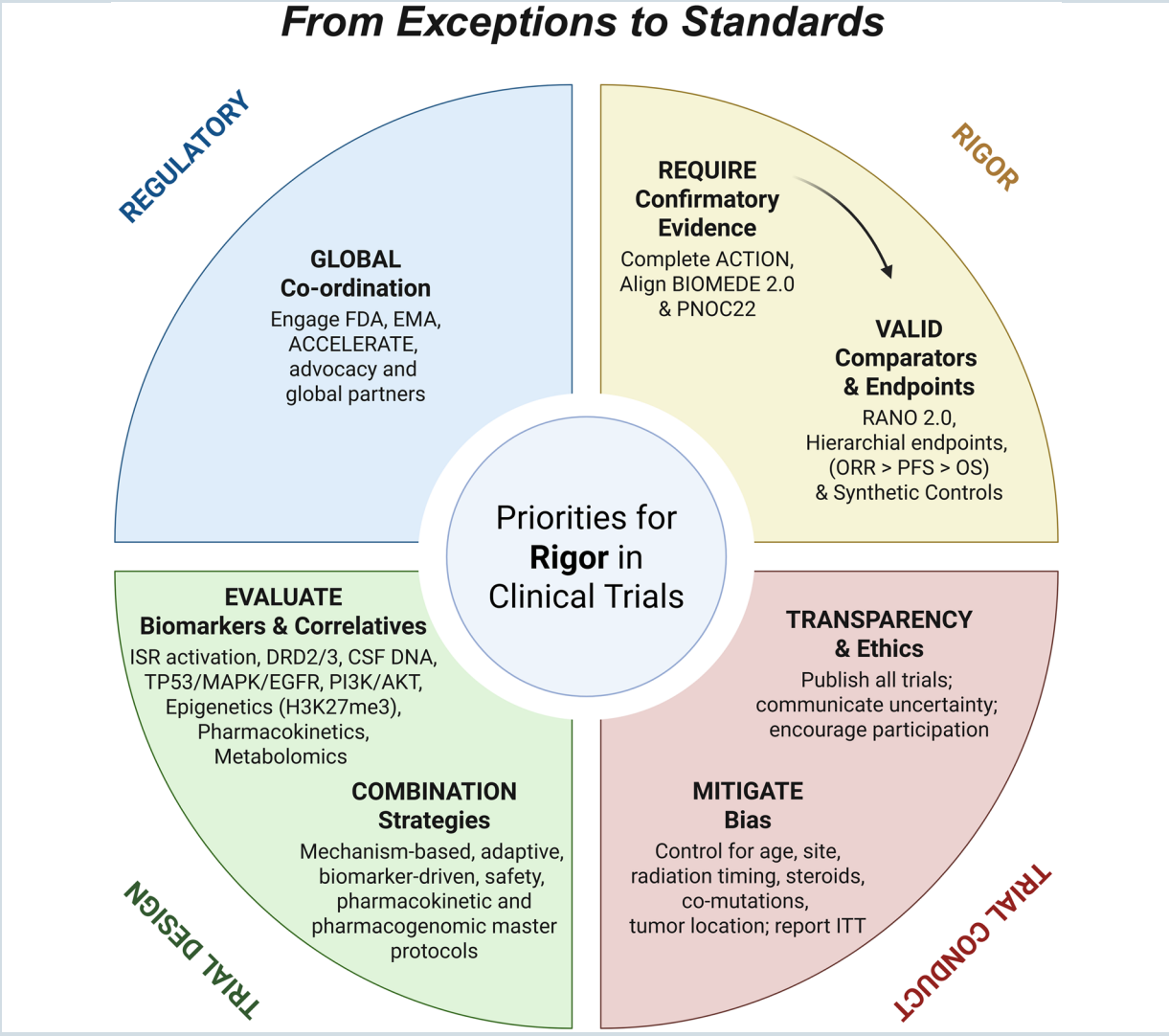

Figure 3. Conceptual framework outlining proposed strategies to strengthen future diffuse midline glioma clinical trials and regulatory pathways. The figure highlights integration of regulatory coordination, validated clinical and biological endpoints, biomarker-driven patient evaluation, mitigation of trial bias, mechanism-based combination therapies, and ethical transparency. Together, these components are presented as a pathway to improve trial design, interpretation, reproducibility, and global clinical impact.

progressive brain tumors may justifiably use radiographic response as an early indicator of therapeutic activity, provided confirmatory studies are actively conducted to verify survival benefit.

Ethically, accelerated approval in this context balances compassionate access with scientific rigor. It offers patients with a fatal diagnosis an option beyond radiation alone, while maintaining the obligation to generate confirmatory evidence. Yet the notion that DIPG and related DMGs are too rare for rigorous study has itself contributed to the scarcity of high-quality data. The FDA's decision therefore carries a dual message: it signals to advocates, clinicians, and industry that the agency is open to ORR-based endpoints for "accelerated" approvals, but it should not be misinterpreted as justification for lowering the bar. Rather than treating DMG as an exception to evidentiary standards, we should see it as a test case for how well-designed, collaborative studies can definitively answer therapeutic questions even in uncommon diseases (Figure 3).

Broader Implications

Beyond its immediate regulatory significance, dordaviprone's approval carries broader clinical, psychological, and structural implications for the DMG landscape. It provides a preliminary clinical break on the long-standing "therapeutic nihilism" surrounding DMG by demonstrating that systemic agents can achieve meaningful biological and radiographic effects in this disease. This paradigm shift transforms how both families and clinicians perceive the treatment landscape, from inevitability to incremental progress.

The decision also lays the groundwork for future randomized trials that avoid placebo-only control arms, a major ethical and logistical barrier in pediatric neuro-oncology. Future studies are now more likely to test combination regimens (e.g. dordaviprone ± a second investigational agent) against active comparators, increasing acceptability to patients and families (Figure 3). Moreover, the regulatory precedent is expected to stimulate industry investment and academic-industry collaboration, encouraging development of rational combination therapies and biomarker-driven trial designs. Work investigating novel combinations will seek to encompass both newly diagnosed and recurrent populations, pending the results of confirmatory phase 3 studies in the newly diagnosed setting such as the ACTION and BIOMEDE 2.0 (NCT05476939) trials.

Finally, the approval broadens the conceptual framework for DMG therapy beyond the traditional radiation-only paradigm, legitimizing exploration of metabolic, mitochondrial, and epigenetic interventions within structured clinical trials. As confirmatory data from the ACTION study and subsequent efforts mature, the legacy of dordaviprone may extend far beyond its individual efficacy, ushering in a new regulatory and therapeutic era for DMG and related midline gliomas.

Counterpoint: A Premature and Risky Approval

Despite encouraging signals, the current evidence base for dordaviprone falls short of a gold-standard randomized phase 3 demonstration of benefit. While phase 2 studies have suggested preliminary signals of efficacy, much of the supportive data derive from retrospective and uncontrolled cohorts, leaving the program vulnerable to selection effects and immortal time bias.[29] ORRs appear modest, and although responses (when they occur) tend to be durable (median duration of response ~11.2 months), durability alone cannot substitute for randomized confirmation of clinical benefit. As such, there has been no published phase 2 data definitively supporting its use in DIPG and spinal DMG to date.

Generalizability is another constraint. The most mature datasets leading to approval disproportionately involve adult thalamic tumors, while efficacy in DIPG and spinal cord DMG remains uncertain, despite these populations being included in the accelerated FDA approval. Practical barriers including low incidence, anatomical heterogeneity, and difficulties adjudicating response in infiltrative midline disease, have limited precise ORR estimation in these subgroups and complicated historical benchmarking. Following consultation with the FDA, a pre-specified pooled subset of 50 patients with recurrent (based on imaging or clinical symptoms), measurable disease treated >3 months post-radiation (to reduce pseudoprogression), was assembled across studies to estimate ORR and duration of response, but this strategy cannot fully eliminate residual bias and included only four children, limiting the strength of pediatric-specific evidence.

Methodologic evolution further complicates interpretation. Initial analyses used RANO HGG/LGG criteria; subsequent re-analysis with RANO 2.0, developed in part to address mixed enhancing/non-enhancing gliomas, yielded response assessments more tailored toward DMG biology. Even so, cross-framework comparisons and post hoc harmonization introduce uncertainty. Additional confounders include the prognostic impact of age and tumor location, guarantee-time bias from variable intervals between radiation and dordaviprone initiation, and bevacizumab use, which can alter vascular permeability and confound radiographic response. Although prior bevacizumab was allowed (with appropriate washout), patients were not evaluable for response if they received bevacizumab during treatment.

Sources of Data Informing the FDA—What the FDA Saw Versus What Is Published

As requested by the FDA, the approval package relied on an integrated analysis pooling data across multiple studies, including the initial single-arm phase 2 trial that was explicitly designed to detect an efficacy signal of efficacy. An exceptional responder with an H3K27M mutation in that phase 2 program catalyzed the addition of a molecularly defined H3K27M cohort and the rapid opening of further trials in both children (phase 1 first) and adults. In a cancer with extreme unmet need and limited feasibility for large, rapid randomized studies, the FDA judged a pooled, prospectively specified analysis to be the most expeditious pathway to evaluate antitumor activity while a definitive trial matured. In parallel, the ACTION trial was launched as a rigorous, phase 3 confirmatory study in non-recurrent patients (well powered and methodologically robust) though notably excluding DIPG and spinal cord DMGs, a significant gap with clinical implications.

A key question is whether it is appropriate to base approval on an integrated dataset when individual trials have not all been fully reported. It is important to clarify that the FDA had access to the complete, patient-level data across contributing studies, including elements not yet in the public domain. While this mitigates regulatory blind spots, it does not substitute for comprehensive peer-reviewed, intent-to-treat publications that allow clinicians and researchers to independently scrutinize design choices, analysis populations, and sensitivity analyses.

The datasets include heterogeneous populations spanning newly diagnosed and recurrent disease, wide age ranges, and diverse prior therapies. The response analysis focused on recurrent, measurable H3K27M-mutant tumors treated more than 3 months after radiotherapy to minimize pseudoprogression, while newly diagnosed patients were reported separately and were not part of the approval dataset. Such heterogeneity is expected in a rare disease but limits external validity and subgroup interpretation.

Regulatory Considerations

The accelerated approval of dordaviprone establishes an important but delicate regulatory precedent for neuro-oncology. It acknowledges that in rare, lethal diseases such as DMG, the evidentiary bar must be both realistic and rigorous: high enough to ensure true clinical value but flexible enough to enable access. Historically, oncology

approvals often required ORR exceeding 50% to justify accelerated authorization, an unrealistic threshold in low-proliferative or diffusely infiltrative tumors like gliomas. Neuro-oncology investigators have long argued for a more nuanced standard that contextualizes response magnitude with disease lethality, unmet need, and toxicity profile. In this respect, dordaviprone's modest but durable responses, combined with its low incidence of severe side effects, may represent an appropriate recalibration of risk-benefit expectations for DMG.

Whether this decision will encourage or discourage industry participation remains uncertain. On one hand, it signals regulatory openness to single-arm datasets and surrogate endpoints in rare CNS tumors, which could stimulate new investment and drug development. On the other, while accelerated approval enables earlier market access and potential patient benefit, it still requires a confirmatory phase 3 randomized trial to verify clinical efficacy. Sponsors are aware of these obligations; the key challenge lies not in discouragement, but in ensuring that confirmatory studies, often phase 3 in design, are feasible, adequately powered, and already well advanced at the time of approval.

Historical precedents highlight both the promise and the pitfalls of this pathway. Temozolomide gained accelerated approval for glioblastoma based on early-phase data and was subsequently validated by the landmark phase 3 trial, transforming standard of care. Conversely, bevacizumab also received accelerated approval for recurrent glioblastoma but failed to improve survival in randomized phase 3 trials, prompting regulatory reassessment. The lesson is clear: accelerated approval can catalyze therapeutic progress, but it demands rigorous follow-through to prevent premature conclusions and ensure long-term credibility in the field. The ongoing BIOMEDE 2.0 trial, which randomizes newly diagnosed DMG and DIPG patients between everolimus and dordaviprone in combination with radiotherapy, may provide an opportunity to either validate the single-arm signals that underpinned accelerated approval or challenge them through a head-to-head design.

Accelerated approval introduces ethical challenges that extend beyond regulatory considerations. Families may conflate the FDA approval with proven efficacy, leading to unrealistic expectations and disappointment when benefit does not occur. While accelerated approval signals preliminary evidence of activity, it does not confirm survival benefit, and response rates remain modest. Clinicians must communicate this uncertainty clearly, emphasizing that many patients may not respond and that confirmatory data are still pending.

The approval has also created a transitional access gap, in which some families, particularly those outside trial networks, pursue private or foreign sources of dordaviprone at significant financial and emotional cost.[30] This inequity underscores the need for transparent global supply frameworks and fair access policies. At the same time, broad post-approval availability could undermine trial enrollment, though the ACTION trial has been structured to focus largely on non-US accrual to mitigate this effect.

Cost and access remain major concerns. As with other orphan indications, high pricing and variable reimbursement or insurance coverage may deepen disparities between patients and families who can access the drug and those who cannot. Regulators, sponsors, and advocacy groups must work together to ensure that expanded access does not become selective access and that participation in confirmatory trials remains both feasible and ethically supported.

The ethical balance of accelerated approval depends on transparent communication, equitable access, and continued scientific engagement. Dordaviprone offers an opportunity for patients with a fatal cancer, but without careful stewardship, it could also distort incentives, slow evidence generation, and erode public trust. The neuro-oncology community must treat this approval as a beginning rather than an endpoint, ensuring that hope is matched by evidence and that access is sustained by robust clinical data.

Balancing Innovation and Evidence

The accelerated approval of dordaviprone reflects profound unmet need and sustained patient advocacy in DMG. The decision is explicitly conditional and must be confirmed in follow-up studies, most importantly the ACTION trial, with complementary insights anticipated from BIOMEDE 2.0 and PNOC022 (NCT05009992). Until those data are available, a stance of cautious optimism grounded in rigor is warranted.

Progress will depend on stronger comparators and clearly defined endpoints (Figure 3). International DMG registries with more than one thousand patients such as the International DIPG/DMG Registry and Repository (IDIPGR, NCT03101813) might be able support matched historical or synthetic controls when randomization is not feasible. However, these registries will require augmentation of data collection to fulfill regulatory requirements of synthetic control data. Harmonizing PFS definitions and accounting for the impact of re-irradiation on OS are essential. Continued collaboration among regulators, industry, advocacy groups, clinical trial networks, and academic investigators through mechanisms such as the FDA, EMA, and ACCELERATE[31] can maintain consistency and transparency for rare pediatric and young adult brain tumors.

Phase 3 trials with survival endpoints remain the ideal, while recognizing that rare diseases may sometimes require integrated analyses or prespecified external control arms. The ACTION study is the confirmatory backbone for thalamic DMGs, with the BIOMEDE 2.0 trial powered to address the same question specifically in DIPG patients. The FDA's accelerated approval, granted conditionally on an early, requested integrated analysis, should not be viewed as evidence of flawed trial design. Randomization in initial phase 2 studies was inherently challenging in the absence of an established systemic standard of care, limited patient numbers, and across both pediatric and adult populations.

To translate access into durable benefit, clinical studies should be paired with robust correlative science to identify responders and resistance mechanisms, with clear communication of limitations to families and full intent-to-treat publication to avoid selective reporting. At present in the recurrent setting, the response rate is about 20%, meaning many patients will not benefit, and confirmatory results are pending. Clinicians should explain that approval was based mainly on adult data, while recognizing that families of

children with DMG may still wish to pursue treatment given the lack of alternatives.

This approval is both historic and cautionary. It is the first systemic therapy authorized for H3K27M-altered DMG, offering real momentum while highlighting the tension between urgency and evidence. Future success will hinge on confirmatory outcomes, mechanism-informed combinations, and avoiding past pitfalls in glioma drug development. Until phase 3 results are positive and regulatory review is complete, dordaviprone should not be considered standard of care particularly for DIPG. All completed studies should be published in full to align practice with the totality of evidence. Members of the pediatric neuro-oncology community have voiced concerns about design and interpretation of pivotal trials and ask for more engagement by sponsors to address these issues. Sustained, bidirectional communication between investigators, regulators, and families will be essential to advance both patient care and the scientific foundation on which it rests.

Keywords

accelerated approval | ACTION trial | diffuse midline glioma | dordaviprone | H3K27M mutation | ONC201 | surrogate endpoints | the FDA

Lay Summary

The United States (US) Food and Drug Administration (FDA) recently granted accelerated approval to dordaviprone (ONC201, Modeyso™) for patients with H3 K27M–altered diffuse midline glioma, a rare and aggressive brain tumor with very few treatment options. This Point/Counterpoint editorial discusses what this decision means for science, regulation, and patient care. Accelerated approval allows the FDA to make promising treatments available sooner for serious diseases based on early signs of benefit, such as tumor shrinkage or how long patients respond to treatment. However, additional studies are still required to confirm that the drug truly improves outcomes. In this case, the approval was based on early studies and expanded-access programs that showed the drug may help a subset of patients. Important questions remain. Most of the data used for approval came from non-randomized studies, and it is unclear how well the drug works in newly diagnosed patients or in related tumors such as diffuse intrinsic pontine glioma (DIPG) and spinal cord tumors. We argue that this approval should be seen as conditional, an important step that may speed up research on drug combinations, biomarkers, and better clinical trials, while still requiring strong evidence. The ongoing ACTION trial (NCT05580562) will be critical for confirming the benefit of the drug and guiding how it should be used in practice.

Conflict of Interest Statement

M.K. reports grants or contracts from BMS, AbbVie, BioNTech, CNS Pharmaceuticals, Daiichi Sankyo Inc., Immorna Therapeutics, Immvira Therapeutics, and Personalis, Inc.; received consulting fees from JAX lab for Genomic Research, George Clinical, Menarini Stemline, and Servier; received honoraria from GSK; and is on the scientific advisory boards of George Clinical, Siren Biotech., and a data safety monitoring boards for BPG Bio and The University of Pennsylvania Center for Cellular Immunotherapies; RGWV owns equity in Boundless Bio, Inc; M.D.D. is a parent to a child lost to diffuse intrinsic pontine glioma (DIPG), and the Founder and Director of the not-for-profit charity, RUN DIPG Ltd. I.A.-R. has received research funding from Chimerix (Inst), Astex (Inst), Taiho (Inst), and GSK (Inst); advisory fees from Servier and Boehringer Ingelheim. E.B. sits on the advisory boards for Alexion, Novartis, Gilead, and Servier International. J.R.H. receives honoraria for consultation from Bayer and Alexion and sits on the advisory board for Servier International. K.S. reports consulting fees, an equity interest, grants paid to his institution and research contracts from Adaptin Bio, which has licensed intellectual property from Duke related to the use of Brain Bi-specific T cell Engagers and combination autologous lymphocyte therapy. S.M. reports grants or contracts from BMS, Regeneron, Beigene, Kazia, Chimerix, CV Bio, Novartis, Pfizer, DayOne Bio. She also is a member of the SAB for Day One Bio. P.Y.W. has received research support from Astra Zeneca, Black Diamond, Bristol Myers Squibb, Chimerix, Eli Lilly, Erasca, Global Coalition For Adaptive Research, Kazia, MediciNova, Merck, Nerviano, Novartis, Philogen, Quadriga, Servier, and VBI Vaccines and has served on the advisory board or as a consultant to Anheart, Alexion/Astra Zeneca, Black Diamond, Chimerix, Day One Bio, Fore Biotherapeutics, Genenta, Glaxo Smith Kline, Kintara, Merck, Mundipharma, Novartis, Novocure, Nuvation Bio, Prelude Therapeutics, Sapience, Servier, Symbio, Tango, Telix, and VBI Vaccines.

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Point-Counterpoint