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EDITORIAL

ONC201 (Dordaviprone): review of evidence to date in diffuse midline glioma, hope or hype?

Jordan R. Hansford [a,b,c], Neevika Manoharan[d,e,f], Gauthier Bouche [g], Vijay Ramaswamy[h,i,j], Nada Jabado[k] and Eric Bouffet [l]

[a]Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital, Adelaide, SA, Australia; [b]Paediatric Neuro-Oncology, Cancer Precision Medicine, South Australia Health and Medical Research Institute, Adelaide, SA, Australia; [c]South Australia ImmunoGENomics Cancer Institute, University of Adelaide, Adelaide, SA, Australia; [d]Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia; [e]Children's Cancer Institute, Lowy Cancer Centre, UNSW Sydney, Kensington, NSW, Australia; [f]School of Clinical Medicine, UNSW Medicine & Health, UNSW Sydney, Kensington, NSW, Australia; [g]The Anticancer Fund, Meise, Belgium; [h]Developmental and Stem Cell Biology, Labatt Brain Tumor Research Centre, The Hospital for Sick Children, Toronto, Canada; [i]Division of Hematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada; [j]Departments of Medical Biophysicsand Pediatrics, University of Toronto, Toronto, ON, Canada; [k]Department of Pediatrics, McGill University, RI-MUHC, Glen Site, Montreal, QC, Canada; [l]The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

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1. Introduction

High-grade gliomas account for 10–15% of tumors of the central nervous system in the pediatric population. Diffuse midline glioma (DMG) accounts for the largest proportion of high-grade glioma and are almost universally fatal with a 2 years survival rate of less than 10% [1]. Radiotherapy is the only treatment that has shown efficacy, although transient, and no chemotherapy agent or targeted treatment has demonstrated an impact on survival. Oncogenic signaling cascades in DMG are promoted by the loss of trimethylation at lysine 27 (K27) of histone H3 resulting in a methionine to lysine substitution (H3K27M) in either *HIST1H3B* (H3.1) or *H3F3A* (H3.3) genes or through the overexpression of EZH inhibitory protein (*EZHIP*) in patients with wild-type H3 [2–4].

Since 2017, several articles have presented evidence suggesting clinical efficacy and responses to the dopamine receptor D2 (DRD2) antagonist ONC201(Dordaviprone) in diffuse midline glioma (DMG) [5–7]. This medication, with seemingly few side effects and a simple administration schedule has generated a great deal of excitement since early single-case studies reported the efficacy of this agent in this otherwise incurable tumor type.

ONC201 (also known as TIC10 and NSC350625) was initially patented in 1973. This is a brain penetrant imipridone recently identified as a DRD2 antagonist [8]. In primary screening of anti-cancer compounds in colon cancer cell lines, it was identified as a key effector of the TNF-related apoptosis inducing ligand (TRAIL) immune surveillance system [9,10]. ONC201 led to a sustained upregulation of TRAIL in colon cancer tumor cell lines through inhibition of Akt and MEK leading to inhibition downstream of extracellular signal-regulated kinase (ERK). This inhibition leads to downstream Foxo3a dephosphorylation and the ability to translocate to the nucleus and upregulate the TRAIL promoter leading to widespread TRAIL-mediated apoptosis [10]. This led to a flurry of activities given its potential clinical utility in *TP53* mutant tumors and identified a wide range of tumors where the agent promotes tumor regression via apoptosis including breast, colon and brain cancers [11–13]. Since these initial signals, ONC201 mechanism of action has been further investigated and found to stimulate the mitochondrial caseinolytic protease P enzyme impairing oxidative phosphorylation and inducing cell death [14–16].

With progressive pharmacological studies in the drug development process, it was noted that the linear, inactive compound that was originally patented was indeed different to the active, angular form found to have anti-cancer effects (reviewed in [17]). This finding led to much controversy and dispute around intellectual property.

2. Body

The initial evidence of activity of ONC201 in patients with DMG comes from a phase II study conducted in 2016 in adult patients with recurrent glioblastoma. A 22-year-old patient with a recurrent secondary glioblastoma harboring a H3.3 K27M mutation achieved a partial response after 7 doses that was sustained for >6 months [18]. Soon after, protocols were developed to confirm the potential of ONC201 in H3.3K27M DMG. Case reports of response in young patients with H3-mutated midline glioma began to emerge [19,20], raising hopes that this agent would be the first to make a difference in this otherwise fatal tumor.

However, two ONC201 studies were open in a limited number of US institutions, and access to this agent has been limited or impossible in many countries internationally (Summarized in Table 1). This has led to a rush from desperate patients and families looking to access this agent through

CONTACT Eric Bouffet eric.bouffet@sickkids.ca The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada

Table 1. Summary of ONC201 studies in diffuse midline glioma to date.

Study	Phase	Number of Patients	Unpublished Patients	Age (Median Age)	Disease	Dose ONC201	Date of first treatment	Comments
Arrillaga et al [18]	2	17		≥18 yrs 57 (22-74)	Recurrent IDH1/2 WT GBM	625 mg weekly	Jan 2016	1 patients confirmed H3K27M
Arrillaga-Romany et al [21]	2	20 in Non-Surgical Arm 6 in Surgical		≥18 yrs Nonsurgical 55 (20-74) Surgical 65.5 (47-69)	Recurrent IDH1/2 WT GBM	625 mg weekly	March 2017	3 nonsurgical patients with confirmed H3 K27M
ONC201-006	2	72	62	≥16 yrs	Recurrent GBM or Grade IV with or without K27M	625 mg weekly	Jan 20, 2016	
ONC201-013	2	50	21	≥18 yrs	Recurrent HGG with H3 K27M	625 mg once every week	Oct 31, 2017	
Gardner et al [22] ONC201-014	1	Total 125 30 Presented in (5)	95	2-18	Recurrent H3K27M glioma; Newly diagnosed DIPG Thalamus Brainstem	125-625 dosed on weight once weekly	Jan 20, 2018	
ONC201-016	N/A	10	9	≥18	H3 K27M DMG	625 mg weekly	Nov 2, 2017	Single patient Compassionate Access
ONC201-018 Chi et al [19]	N/A	Total 117 41 Presented in (5) 18 Presented in [19]	58	≥3 yrs	Recurrent H3K27M DMG ≥10 kg	625 mg weekly ≥18 yrs of age; body weight dosed <18 yrs of age	Jan 31 2019	Expanded access program
Venneti et al [5]	N/A	71 014 = 30 018 = 41	N/A	014 – 8.2 yrs (2-21) 018-23.7 (4-58)	Thalamus 014 $n = 11$ 018 $n = 19$ Brainstem 014 $n = 19$ 018 $n = 22$	625 mg weekly ≥18 yrs of age; body weight dosed <18 yrs of age	Jan 20, 2018	Concurrent Bevacizumab 014 = 5 018 = 8
Arrillaga et al [6]	N/A	Total 50 006 = 10 013 = 29 014 = 2 016 = 1 018 = 8	N/A	30 (8-70)	Recurrent H3K27M non-pontine; non- spinal DMG	625 mg weekly ≥18 yrs of age; body weight dosed <18 yrs of age	Jan 20, 2016	

alternative routes. Andre et al. highlighted some of these complexities recently [23]. To accommodate for this lack of availability, utilizing country-specific legal exceptions around individual patient care (*individueller Heilversuch*), German oncologists began prescribing locally synthesized Dordaviprone to families seeking the drug, including non-German families who traveled to Germany to access the medication at significant cost. In December 2023, the pharmaceutical company, Chimerix, which produces ONC201 as part of the official clinical trials, filed a lawsuit against the German company to cease selling ONC201. An expanded access program through Chimerix was announced for US and European patients only. However, 6 years after the opening of the first clinical trials of ONC201 in DMG, the data supporting its activity in an otherwise terminal disease have been slow to prove or disprove its clinical utility despite widespread desire to access and use this medication internationally.

In 2022, Gardner et al. reported the results of a phase I pediatric study on ONC201 in children and adolescents with DMG (Table 1). This trial included 22 patients, including 20 with a biopsy proven H3K27M mutated tumor [22]. The most common tumor sites were the pons in 13 patients, and the thalamus in 5. Six patients had recurrent disease and 16 were enrolled after completion of radiation treatment. This study recommended the use of the adult 625 mg weekly dose scaled by body weight. In the group of 16 patients treated before recurrence, the median progression-free survival (PFS) was 20.4 weeks and the median overall survival (OS) was 53.8 weeks. Assessment of tumor response to ONC201 was not possible due to the preexisting radiotherapy treatment. In a group of 6 patients with recurrent tumor the median PFS was 12.6 weeks. The authors concluded that several factors inherent to the phase I design of the study precluded efficacy conclusions.

In a publication one year later, Venneti *et al* pooled together data from two early-phase studies: ONC201–014 (NCT03416530) and ONC201–018 (NCT03134131) [5]. The outcome of 71 unique patients (30 from ONC201–014 [22]; and 41 patients from ONC201–018) were described and, from this analysis, the authors concluded that treatment with ONC201 results in a significant improvement in the PFS and OS of patients with either non-recurrent or recurrent DMG. The authors used a comparison with a cohort of 373 historical control patients. Their conclusion was that ONC201 was the first monotherapy to improve the outcome in H3K27M mutant DMG beyond radiation. More recently, Arrillaga-Romany *et al.* reported on a highly selected group of 50 patients, mostly adults (46/50) with relapsed/progressive DMG, excluding spinal and diffuse intrinsic pontine gliomas (DIPG), enrolled across five clinical trials or expanded access programs (EAP) namely ONC006 (NCT02525692), ONC013 (NCT03295396), ONC014 (NCT03416530) [22], ONC016 (single patient compassionate use program) and ONC018 (NCT03134131) suggesting a response to therapy in this cohort.

Upon further scrutinizing the clinical data presented, the conclusions from both recent articles may overly portray an optimistic view due to selection bias. Notably, most patients in these clinical trials and EAP have not been reported on and the publications are notable for the selected inclusion of a cohort of patients without reporting on the outcomes of the entire cohort. Both studies included newly diagnosed post-irradiation patients before progression, yet lacked a uniform time restriction from diagnosis to drug initiation. The timing of ONC201 commencement post-radiotherapy ranged widely, from 0.5 to 18 months in Venneti et al [5] and from 3 to 103.6 months in Arrillaga-Romany et al [6]. Trials enrolling patients' post-radiotherapy and any time prior to progression introduce an inherent lead time bias. An important limitation of collectively reporting on multiple patients across different trials and EAP is that some of the patients described had been pre-treated with other conventional and experimental therapies, a further potential confounder in reporting on201 the efficacy of ONC201. Notably, some patients were already long-term survivors before commencement of therapy, affecting overall survival curves, a phenomenon called immortal-time bias or guarantee-time bias [24]. Although sensitivity analyses were performed (such as removing patients with survival of less than 3 months from the historical cohort), these do not overcome the potential inherent biases of the ONC201 studies. In addition, while the mutation status of the historical control group and the study population was relatively balanced (69% H3.3 mutations in ONC201 treated patients versus 79% in controls), the cohorts differed by their age (median 13.2 years old in ONC201 patients versus 7.3 in controls) and their anatomic location (42% thalamic in ONC201 treated patients versus 24% in controls). As older age and thalamic location is associated with longer survival in DMG patients, the conclusions of the authors appear premature and unjustified [25]. When adjusting for these biases in progression-free survival and OS analyses, outcomes align closely with historic controls.

Each year, over 300 children are diagnosed with DIPG in the United States, and likely more in the European community [1]. A multicentre international clinical trial of ONC 201 would take less than a year to demonstrate benefit in this uncurable disease. In this context, it is surprising to see these 2 publications that needed to combine patients recruited in five different clinical trials or expanded access programs to suggest a benefit. In addition, while these studies enrolled a total of 374 patients, only 71 were analyzed in the publication from Venneti and 50 in Arrillaga-Romany's report. Reports on clinical trials should include all enrolled patients from an intent-to-treat perspective, and the rationale for the exclusion of patients from survival analyses should be clearly outlined within the robust statistical methodology of early-phase clinical trial design.

Furthermore, it is concerning that these studies included patients who received additional treatment in their reported responder group. From our review, at least 13 patients reported in Venneti et al. that were included in the response and radiographic assessment (Figure 2 Venneti) were reported to have been given bevacizumab, an agent known to yield improved imaging and responses without improving outcome [5]. Indeed, the glioblastoma literature is fraught with Phase 2 studies suggesting efficacy that are never realized in Phase 3 studies where patient selection bias is less evident. Given these issues, we are concerned the evidence provided thus far on the use of this agent, is no more compelling than previous DMG related studies.

Overall, these results do not shed more light on the potential activity of ONC201 in DIPG patients, leaving the international pediatric neuro-oncology community frustrated, as the inappropriate design of these trials had been flagged early on. There is some concern that the results presented in these recent publications may be used to file for ONC201 approval in H3K27M-DMG patients to the US FDA, while the evidence for a possible benefit is associated with potential biases. With time and additional studies, this agent may show efficacy. However, in order to describe better the true effect of ONC201 on this devastating condition, clinical trials that are controlled for crucial endpoints such as allowing for enrollment after prior therapies and controlling the time from radiation commencement will be fundamental and have been requested from the international neuro-oncology community since 2018. Furthermore, entire study cohorts need to be assessed and published. ONC013 was a phase II study with a primary endpoint to determine the best overall response rate by RANO yet remains unpublished worldwide. In addition to the conduct of clinical trials with more robust methodology, it is prudent that the results of these studies are reported on in the entirety and not subject to the selection bias of only reporting on patients whom have had a clinical or radiological response. Adult patients and parents of children with DMG are searching for any sort of hope, and a rush toward obtaining ONC201 is already underway, more so with the media's interpretation and dissemination of the 2 recent publications in prestigious medical journals. This serves as a reminder that patients should primarily be offered access to experimental treatments in well-designed trials. Moreover, using or approving a drug without substantial evidence of efficacy has the potential to cause more harm than good. The neuro-oncology community needs to respond to the legitimate urgency from parents and patients with a firm commitment to ensure that investigational treatments are offered in well-designed trials until proven clinically effective.

3. Expert opinion

ONC201 (Dordaviprone) as a potential treatment strategy for patients with DMG has undoubtedly garnered interest, from clinicians, researchers, patients and families alike. The recent publications suggesting potential efficacy of this agent in a small number of patients should prompt robust scientific methodology to be utilized to establish whether this agent truly has a therapeutic signal in this incurable disease and if it does, which patients stand to benefit. The data, as it is presented and published to date, does not meet the metric to justify the conclusion that 'ONC201 is the first monotherapy to improve outcomes in H3K27M mutant DMG beyond radiation.' This conclusion carries with it the expectation from patients and families that finally hope for cure in this devastating disease has been promised and unfortunately, the data presented does not substantiate this expectation.

ONC201 deserves to be evaluated in well-designed, rigorous trials that are appropriately powered to determine efficacy, or conversely, futility. Two current trials, one via the Pediatric Neuro-Oncology Consortium, PNOC022 (NCT05009992) and the other, an international Phase 3 randomized, placebo-control study (NCT05580562) of the agent in non-pontine DMG will hopefully answer these crucial questions. Of equal importance, is the understanding that when these trials are reported, the neuro-oncology community must demand that the results are presented within established paradigms for clinical trials that include reporting on all patients (regardless of response), avoiding inherent biases and ensuring the conclusion is validated by the results presented. Although it is hoped that with time a signal of efficacy will be seen with ONC201 in DMG, of concern is the fact that significant numbers of patients with DMG have been treated with ONC201 since 2016 and to date, the pediatric neuro-oncology community has failed to determine whether this treatment is efficacious. This must be established with urgency prior to international regulatory bodies considering the approval of this agent and its widespread adaptation as standard of care with radiotherapy for this disease.

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J R Hansford receives honoraria for consultation from Bayer and Alexion and sits on the advisory board for Servier International

E Bouffet sits on the advisory boards for Alexion, Novartis, Gilead and Servier International

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ORCID

Jordan R. Hansford http://orcid.org/0000-0001-7733-383X
Gauthier Bouche http://orcid.org/0000-0002-3407-2788
Eric Bouffet http://orcid.org/0000-0002-6832-6539

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