Response to Dordaviprone (ONC201) by Prior Radiotherapy Regimen in Recurrent H3 K27M-Mutant Diffuse Midline Glioma

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Introduction

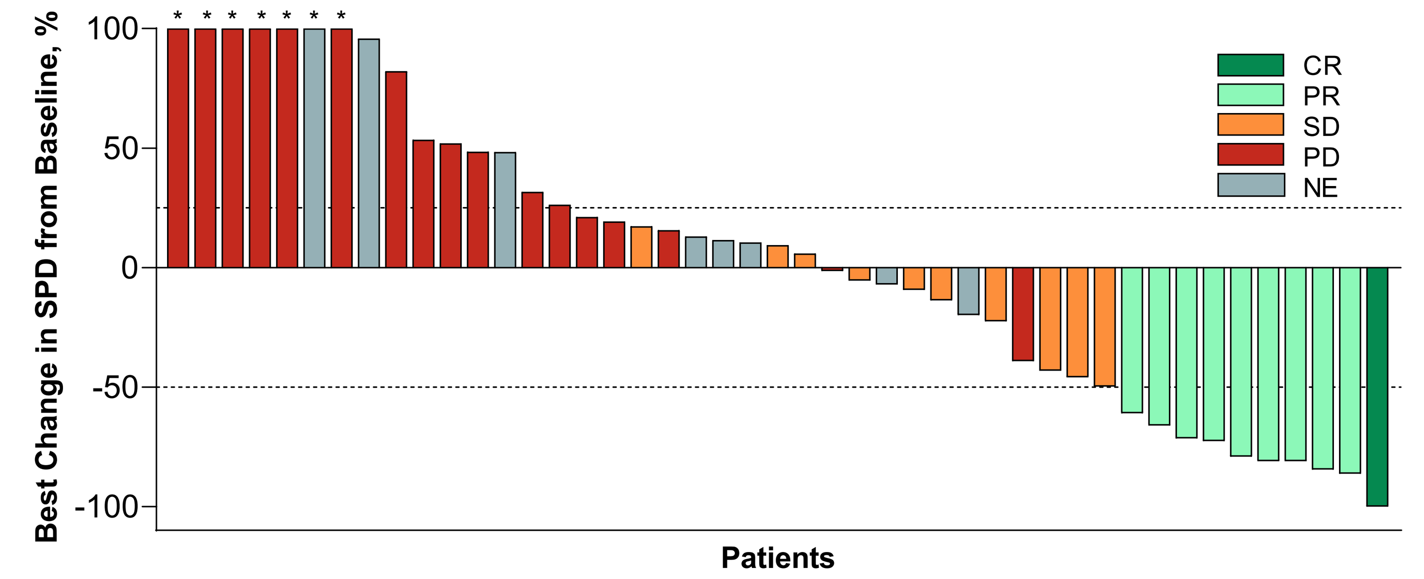
- The H3 K27M mutation is relatively common in diffuse midline glioma (DMG), occurring in up to 80% of pediatric patients and 15-58% of adult patients.[1-3]
- Survival is exceptionally poor; median overall survival is 13.4 months (95%CI, 10.5-15.5), with no substantial difference in 1-year OS when evaluated by age at diagnosis. In contrast, the median OS of patients with H3 wild-type tumors is 4.59 years.[4-5]
- In 2016, the World Health Organization classified H3 K27M-mutant DMG as a distinct form of Grade IV glioma, regardless of histological features.[6]
- Dordaviprone (ONC201) is an oral, blood-brain barrier penetrating, selective small molecule antagonist of dopamine receptor D2 and agonist of the mitochondrial protease caseinolytic mitochondrial matrix peptidase proteolytic subunit.[7-11]
- An integrated analysis of adult (n=46) and pediatric (n=4) patients with recurrent H3 K27M-mutant DMG who received dordaviprone monotherapy in one of five open-label studies was previously conducted (**Table 1 & Figure 1**).[12]
 - Grade 3 treatment-related treatment-emergent adverse events occurred in 20.0% of patients; the most common was fatigue (n=5; 10%); no Grade 4 TR-TEAEs, deaths, or discontinuations occurred.

Table 1. Dordaviprone ORR in Patients with Recurrent H3 K27M DMG

	Total Population (N=50)		
	RANO-HGG[1]	RANO-LGG[2]	Combined HGG/LGG[3]
Overall response rate, n (%) [95%CI]	**10 (20) [10–34]**	**13 (26) [15–40]**	**15 (30) [18–45]**
Complete response, n (%)	1 (2)	0	1 (2)
Partial response, n (%)	9 (18)	6 (12)	9 (18)
Minor response, n (%)	NA	7 (14)	5 (10)
Stable disease, n (%)	10 (20)	8 (16)	7 (14)
Not evaluable, n (%)	8 (16)[4]	11 (22)[5]	11 (22)[5]
Progressive disease, n (%)	18 (36)	14 (28)	13 (26)
Non-applicable, n (%)	4 (8)[6]	4 (8)[6]	4 (8)[6]
Disease control rate, n (%) [95%CI]	**20 (40) [26–55]**	**21 (42) [28–57]**	**22 (44) [30–59]**

[1]Integrated RANO-HGG criteria assessment by dual reader BICR.
[2]Integrated RANO-LGG criteria assessment by dual reader BICR.
[3]Incorporates the best response by RANO-HGG or -LGG criteria for each patient.
[4]Five overall radiographic stable disease accompanied by increase in corticosteroids; three overall radiographic progressive disease accompanied by decrease in corticosteroids.
[5]Eight overall radiographic stable disease accompanied by increase in corticosteroids; three overall radiographic progressive disease accompanied by decrease in corticosteroids.
[6]Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI. BICR, blind independent central review.
HGG, high grade glioma; LGG, low grade glioma; RANO, response assessment in neuro-oncology.

Figure 1. Waterfall Plot of Dordaviprone-treated Patients with Recurrent H3 K27M-mutant DMG (RANO-HGG)


Best Change in SPD from Baseline, %
100
50
0
-50
-100
Patients
CR
PR
SD
PD
NE

CR, complete response; DMG, diffuse midline glioma; DOR, duration of response – defined as from onset of response to progression, defined ; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; RANO–HGG, Response Assessment in Neuro-Oncology–High Grade Glioma; SD, stable disease; SPD, sum product of diameters; TTR, time to response.

- **Corticosteroid response** (≥50% reduction in average daily corticosteroid dose compared to baseline with stable or improved performance score): 46.7% (7/15; 95%CI, 21.3-73.4)[12]
- **Performance score response** (increase in KPS/LPS compared to baseline with stable or reduced corticosteroid use): 20.6% (7/34; 95%CI, 8.7-37.9)[12]
- This sub-analysis of the integrated analysis population was conducted to determine the efficacy of dordaviprone monotherapy in patients with recurrent, H3 K27M-mutant DMG by prior front-line radiotherapy regimen.

Response to ONC201 monotherapy among patients with recurrent H3 K27M-mutant DMG was achieved in patients with diverse front-line radiotherapy regimens.

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Methods

- The treatment regimen and pooled analysis design for this population has previously been reported.[12] Briefly, this integrated analysis included 50 patients (pediatric, n=4; adult, n=46) with recurrent H3 K27M–mutant DMG who received oral dordaviprone monotherapy in four clinical trials or one expanded access protocol.
- 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 endpoint was overall response rate (ORR) by RANO-HGG criteria.
- Radiographic end points were assessed by dual-reader, blinded independent central review.

Results

- Most patients received concurrent chemoradiotherapy (CCRT) + adjuvant (70.0%; **Table 2**).
 - Among patients who previously received adjuvant and/or CCRT, most had received temozolomide (92.8%).
 - Most patients received a standard radiotherapy dose (54-60 Gy) over six weeks.
- Fifteen patients had an objective response by combined RANO-HGG/LGG criteria (**Table 1**).
 - Responses occurred in patients who had previously received CCRT+adjuvant, CCRT, and RT+adjuvant (**Table 3**).
- At least two responders had received proton therapy.
 - The first was an adult patient who received CCRT + Adjuvant (dasatinib) and had a PR by both RANO-HGG and -LGG criteria.
 - The second was a pediatric patient who received RT + Adjuvant (dasatinib, bevacizumab, and everolimus) and had a PR by both RANO-HGG and -LGG criteria.

Results

Table 2. Front-line Radiotherapy Regimen and Dose (All Patients)

	Pediatric Patients (n=4)	Adult Patient (n=46)	All Patients (N=50)
Radiotherapy Dosage, n (%)[a]			
Patients with data available, n	4	38	42
<54 Gy	0	2 (5.2)	2 (4.8)
≥54 Gy	4 (100.0)	36 (94.7)	40 (95.2)
Regimen Received, n (%)			
CCRT + Adjuvant	1 (25.0)	34 (73.9)	35 (70.0)
CCRT	0	8 (17.4)	8 (16.0)
RT + Adjuvant	1 (25.0)	3 (6.5)	4 (8.0)
RT Alone	2 (50.0)	1 (2.2)	3 (6.0)
Prior temozolomide, n^1/n^2 (%)	0/2	43/45 (95.6)	43/47 (91.2)

[a]Percent shown out of total number of patients with dosage data available.
[b]Patient received hypofractionated therapy.
CCRT, concurrent chemoradiotherapy; n^1, total number of patients who received prior temozolomide; n^2, total number of patients who received CCRT and/or adjuvant; RT, radiotherapy.

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Results

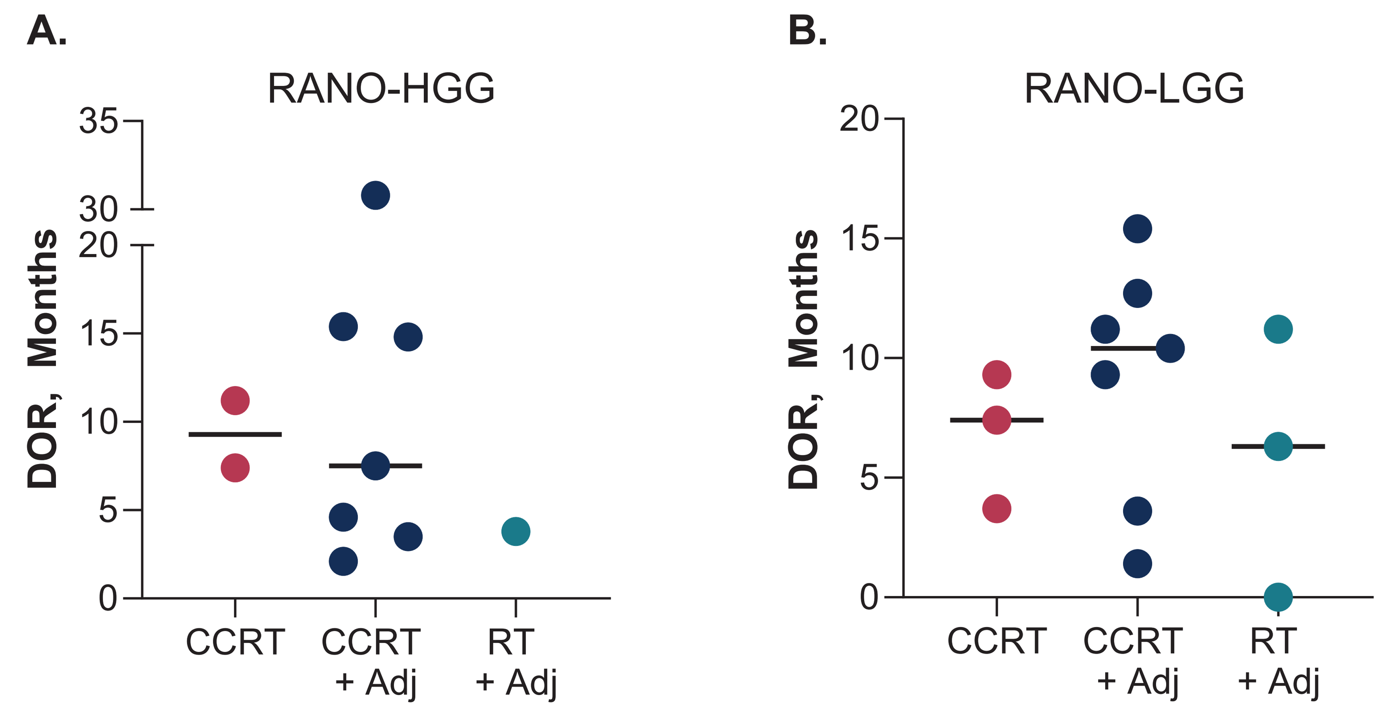
Table 3. Response by Front-line Radiation Regimen[a]

	HGG Criteria		LGG Criteria		HGG/LGG Criteria	
	Responder (n=10)	Non Responder (n=40)	Responder (n=13)	Non Responder (n=37)	Responder (n=15)	Non Responder (n=35)
Regimen Received, n (%)						
CCRT + Adjuvant	7 (70.0)	28 (70.0)	7 (53.8)	28 (75.6)	9 (60.0)	26 (74.3)
CCRT	2 (20.0)	6 (15.0)	3 (23.1)	5 (13.5)	3 (20.0)	5 (14.3)
RT + Adjuvant	1 (10.0)	3 (7.5)	3 (23.1)	1 (2.7)	3 (20.0)	1 (2.9)
RT Alone	0	3 (7.5)	0	3 (8.0)	0	3 (8.6)
Prior temozolomide, n^1/n^2 (%)	8/10 (80.0)	29/37 (78.4)	10/13 (76.9)	27/34 (79.4)	12/15 (80.0)	25/32 (78.1)

[a]Non-responders were patients who did not achieve a MR, PR, or CR. For combined HGG/LGG, non-responders did not have a MR, PR, or CR by both HGG and LGG criteria.
[b]N indicates number of patients who had received a front-line regimen including adjuvant and/or CCRT.
CCRT, concurrent chemoradiotherapy; HGG, high-grade glioma; LGG, low-grade glioma; n^1, total number of patients who received prior temozolomide; n^2, total number of patients who received CCRT and/or adjuvant; NA, non-applicable; NE, non-evaluable; MR, minor response; PD, progressive disease; RT, radiotherapy; SD, stable disease.

- Duration of response appeared similar for patients who had received front-line CCRT, CCRT+Adjuvant, and RT+Adjuvant regimens (**Figure 2**).

Figure 2. Duration of Response by Front-line Radiotherapy Regimen Among Responders by (A) RANO-HGG and (B) RANO-LGG Criteria


A.
RANO-HGG
DOR, Months
35
30
20
15
10
5
0
CCRT
CCRT + Adj
RT + Adj
B.
RANO-LGG
DOR, Months
20
15
10
5
0
CCRT
CCRT + Adj
RT + Adj

Adj, adjuvant; CCRT, concurrent chemoradiotherapy; DOR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; RANO, Response Assessment in Neuro-Oncology; RT, radiotherapy.

Conclusions

- Radiographic responses to dordaviprone in patients with H3 K27M-mutant DMG were observed across various front-line radiotherapy regimens.
- Responses to dordaviprone were observed both in patients receiving front-line photon and proton radiation therapy in both pediatric and adult patients.
- This analysis has limitations, as data on prior front-line radiotherapy treatment modality, dose, and duration were incomplete for some patients.
- The phase 3 ACTION trial (NCT05580562) is currently evaluating dordaviprone in newly diagnosed H3 K27M-mutant diffuse glioma following standard front-line radiotherapy; patients previously treated with temozolomide are eligible provided they have sufficient washout (3 weeks).

Conflicts of Interest

IA-R and **AMH** have received research funding from Chimerix, Inc. **JEA**, **PL**, and **SCR** are employees of and have stock ownership in Chimerix, Inc. **PYW** is a consultant for and has received research funding from Chimerix, Inc. **SLM** has received speakers fees from Chimerix, Inc. **YO** and **SLG** have no relevant COI to declare.

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