CTNI-54

Response by RANO2.0 criteria in ONC201 (dordaviprone)-treated patients with recurrent H3 K27M-mutant diffuse midline glioma

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Introduction

Disease State and Dordaviprone

- The H3 K27M mutation is relatively common in diffuse midline glioma (DMG), occurring in up to 75% of pediatric brainstem tumors patients and up to 60% of adult DMG.[1-4]
- Survival is exceptionally poor, with a median overall survival of approximately 9 months, compared to 4.6 years in patients with H3 K27M wild-type tumors.[5]
- Currently, no effective systemic therapies have proven effective and responses in the recurrent setting are rare.[6-8]
    - 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 (ClpP).[9-13]

Dordaviprone Response Assessment by RANO-HGG and RANO-LGG Criteria

- An integrated analysis of 50 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**).[14]
    - Response was assessed using blinded independent central review (BICR) using both high-grade glioma (HGG) and low-grade glioma (LGG) Response Assessment in Neuro-Oncology Criteria (RANO).
    - Because not all midline gliomas are uniformly enhancing, both RANO-HGG and RANO-LGG were used to quantitatively assess for both enhancing and non-enhancing lesions.[15]
- 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 by RANO-HGG/LGG Criteria in Patients with Recurrent H3 K27M DMG

	Total Population (N=50)		
	RANO-HGG	RANO-LGG	Combined HGG/LGG[a]
ORR, n (%) [95%CI]	10 (20) [10–34]	13 (26) [15–40]	15 (30) [18–45]
BOR n (%)			
CR	1 (2)	0	1 (2)
PR	9 (18)	6 (12)	9 (18)
MR	-	7 (14)	5 (10)
SD	10 (20)	8 (16)	7 (14)
PD	18 (36)	14 (28)	13 (26)
NE	8 (16)[b]	11 (22)[c]	11 (22)[c]
NA	4 (8)[d]	4 (8)[d]	4 (8)[d]
DCR, n (%) [95%CI]	20 (40) [26–55]	21 (42) [28–57]	22 (44) [30–59]

[a]Incorporates the best response by RANO-HGG or -LGG criteria for each patient.
[b]Five overall radiographic stable disease accompanied by increase in corticosteroids; three overall radiographic progressive disease accompanied by decrease in corticosteroids.
[c]Eight overall radiographic stable disease accompanied by increase in corticosteroids; three overall radiographic progressive disease accompanied by decrease in corticosteroids.
[d]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; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; HGG, high grade glioma; LGG, low grade glioma; MR, minor response; NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease; TTR, time to response.

- **Corticosteroid response** (≥50% reduction in average daily corticosteroid dose compared to baseline with stable or improved performance score, confirmed on multiple visits): 46.7% (7 of 15 evaluable patients; 95%CI, 21.3-73.4)[14]
- **Performance score response** (increase in KPS/LPS compared to baseline with stable or reduced corticosteroid use, confirmed on multiple visits): 20.6% (7 of 34 evaluable patients; 95%CI, 8.7-37.9)[14]

RANO 2.0

- RANO 2.0 is a recently established response assessment for glial tumors that is agnostic to WHO grade and replaces prior sub-classification response criteria (**Table 2**).[16]
    - RANO 2.0 is a standard set of criteria recommended for all gliomas.
    - Unified criteria provide assessment of tumors that are enhancing, non-enhancing, and both enhancing and non-enhancing.
- This updated response evaluation was conducted to evaluate response by RANO 2.0 in the integrated analysis population.

Table 2. RANO 2.0 Response Criteria for Tumors with Enhancing and Non-enhancing Components[16]

	Enhancing
CR	**All** the following: 1. Complete disappearance of all measurable enhancing and non-enhancing target lesions and all non-measurable and non-target lesions 2. No new enhancing lesions and no new T2 or FLAIR abnormalities, apart from those consistent with radiation effects 3. Off corticosteroids or on physiologic replacement doses only 4. Stable or improved clinically
PR	**All** the following: 1. ≥50% decrease in SPD, or ≥65% decrease in total volume, of either the contrast-enhancing target lesions or the T2 or FLAIR target lesions, sustained for at least 4 weeks 2. No new enhancing lesions and no new T2 or FLAIR abnormalities,apart from those consistent with radiation effects 3. No progression of measurable and non-measurable disease or non-target lesions 4. Corticosteroid dose not greater than the dose at baseline scan 5. Stable or improved clinically
MR	Applies only to non enhancing disease and can only be determined if the enhancing disease is at least stable. Requires **all** the following: 1. Decrease between 25%-50% in SPD or between 40%-65% of the total volume of non-enhancing target lesions on T2 or FLAIR MRI compared with baseline, sustained for at least 4 weeks 2. No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement 3. No progression of non-measurable disease or non-target lesions 4. Corticosteroid dose not greater than the dose at baseline scan 5. Stable or improved clinically
SD	**All** the following: 1. Does not qualify for CR PR, or SD 2. Stable areas of enhancing and non-enhancing target lesions 3. No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement 4. No progression of non-measurable disease or nontarget lesions 5. Corticosteroid dose not greater than the dose at baseline scan 6. Stable or improved clinically
PD	**Any** of the following: • ≥25% increase in SPD or ≥40% increase in total volume of enhancing or nonenhancing target lesions, or both • On stable or increasing doses of corticosteroids not attributable to radiation effect, edema, or comorbid events • Appearance of a new enhancing or non-enhancing lesions • Appearance of definite leptomeningeal disease • Clear progression of non-measurable lesions • Unequivocal progression of existing non-target lesions • Definite clinical deterioration not attributable to corticosteroid dose or other causes apart from the tumor • Failure to return for evaluation as a result of death or deteriorating condition

CR, complete response, MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of products of perpendicular diameters.

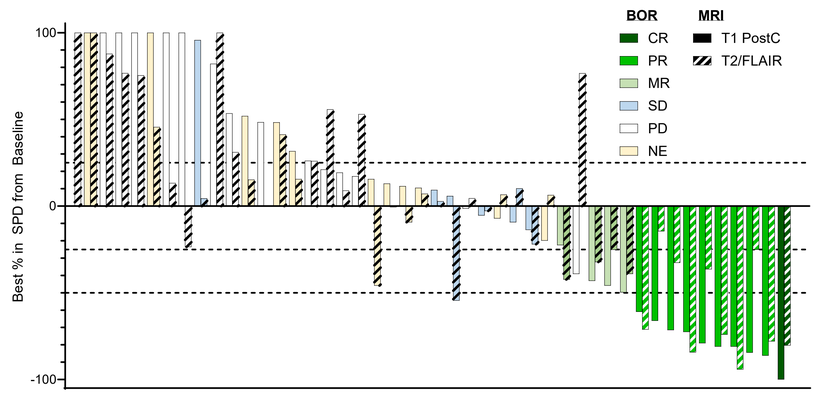
Methods

- The study design, efficacy endpoints including response by RANO-HGG and RANO-LGG criteria, and safety have been previously reported[14]
- Select eligibility criteria included recurrent and/or progressive H3 K27M-mutant glioma (by NGS or IHC), and receipt of prior radiation therapy. DIPG, leptomeningeal spread, cerebrospinal fluid dissemination, and primary spinal tumors were excluded
- Patients received open-label dordaviprone (625 mg or at a dose scaled by body weight for pediatric patients) once-weekly or once every three weeks and were treated at least until progression by RANO-HGG by investigator assessment
- Responses were assessed using RANO 2.0 criteria (**Table 2**)

Results

- Objective response rate by RANO 2.0 criteria was 28.0% (n=14; 95%CI, 16-42), which included one complete response, nine partial responses, and four minor responses (**Figure 1 & Table 3**).
    - One patient who was assessed as a responder by RANO-LGG criteria in the original analysis[14] did not qualify as a responder by RANO 2.0 criteria due to increased T2/FLAIR.
    - Four patients who did not achieve a response by RANO-HGG[14] criteria had minor responses by RANO 2.0.

Figure 1. Waterfall Plot of Dordaviprone-treated Patients with Recurrent H3 K27M-mutant DMG by RANO 2.0 Criteria



BOR, best overall response; CR, complete response; MR, minor response; ; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease.

Table 3. Objective Response Assessment by RANO 2.0

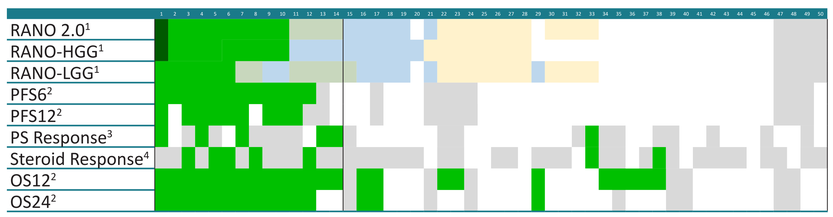
	All Patients (N=50)
ORR n (%) [95%CI]	14 (28.0) [16-42]
BOR, n (%)	
CR	1 (2.0)
PR	9 (18.0)
MR	4 (8.0)
SD	6 (12.0)[a]
PD	15 (30.0)
NE	11 (22.0)
NA[b]	4 (8.0)
Median TTR, months (range)	4.6 (1.6-15.9)
Median DOR, months (range)	10.4 (7.4-15.4)
DCR, n (%) [95%CI]	40% (20) [26, 55]

[a]Includes one patient with unconfirmed response by RANO 2.0.
[b]Three patients did not have on-treatment monotherapy MRIs available for review; one patient was censored prior to first on-treatment MRI
BOR, best overall response; CR, complete response; DOR, duration of response; MR, minor response; NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease; TTR, time to response.

- PFS rates at six and 12 months by RANO 2.0 were 32% (95%CI, 19-47) and 27% (15-41).
- Patients who experienced an objective response (CR/PR/MR) by RANO 2.0 (n=14) were more likely to experience other signs of clinical benefit (**Figure 2**).
    - Complete or Partial Responders by RANO 2.0 (n=10)
        - All 10 patients (100%) had an OS of at least 24 months.
        - Reduction in steroid usage occurred in all four evaluable patients (100%)
        - Improved PS occurred in three of the five evaluable patients (60%)
    - Minor Responders by RANO 2.0 (n=4)
        - All four patients (100%) were alive at 12 months, and two (50%) were alive at 24 months.
        - Reduction in steroid usage occurred in the one evaluable patient (100%).
        - Improved PS occurred in three of the four patients (75%).
- RANO2.0 response as a time-varying covariate was significantly associated with overall survival in a multivariate analysis considering baseline performance score, multiple enhancing target lesions, enhancing tumor size, and number of prior recurrences (HR [95%CI], 0.22 [0.08–0.58]; p=0.0023).
- Responses occurred at a higher rate among patients with a higher performance score and fewer target lesions (**Table 4**)

Results

Figure 2. Patient-Level Endpoints: Objective Response, Progression-Free Survival, Overall Survival and Corticosteroid and Performance Status Responses



RANO[1]	PFS & OS[2]	PS Response[3]	Steroid Response[4]
CR	Yes	Yes	Yes
PR	No	No	No
MR	Censored	NE	NE
SD			
NE			
PD			
NA			

[1]BOR by RANO criteria assessed by BICR. NE if PD with decreasing steroids or SD with increasing steroids. NA if no post-baseline assessments.
[2]PFS ≥6 months/12 months by RANO 2.0 criteria assessed by BICR; OS ≥12 months/24 months. Patients censored if not progressed/alive at last assessment/follow-up prior to cutoff.
[3]Performance status response defined as increase in KPS/LPS compared with baseline, while also having stable or reduced corticosteroid use. Increase must be confirmed at the next analysis time-point. Patients with baseline KPS/LPS ≤80 were evaluable for this analysis.
[4]Steroid response defined as ≥50% reduction in average daily steroid dose compared with baseline or reduction ≤2 mg with stable or improved KPS/LPS. Reduction must be confirmed at the next analysis time-point. Corticosteroids were converted into a dexamethasone equivalent dose. Patients receiving ≥4mg dexamethasone at baseline were evaluable for this analysis.
BICR, blind independent central review; BOR, best overall response; CR, complete response; HGG, high-grade glioma; KPS, Karnofsky performance score; LGG, low-grade glioma; LPS, Lansky performance score; MR, minor response; NA, not applicable; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance score; RANO, Response Assessment in Neuro-Oncology; SD, stable disease.

Table 4. Subgroup Analysis of RANO 2.0 Response by Baseline Characteristics

ORR, n1/n2 (%)	All Patients (N=50)
Age	
<18	1/4 (25.0)
18-<40	9/32 (28.1)
≥40	4/14 (28.6)
Sex	
Female	8/23 (34.8)
Male	6/27 (22.2)
Race	
White	12/39 (30.8)
Other	2/11 (18.2)
Ethnicity	
Hispanic/Latino	1/4 (25.0)
Not Hispanic/Latino	11/41 (26.8)
Unknown	2/5 (40.0)
KPS/LPS	
60-70	1/14 (7.1)
80	8/20 (34.8)
90-100	5/16 (31.3)
Tumor Size	
<10 cm^2	6/22 (27.3)
≥10 cm^2	8/27 (29.6)
Unknown	0/1 (0)
Primary Tumor Location	
Non-Thalamus	3/17 (17.6)
Thalamus	11/33 (33.3)
Multifocal Disease	
No	3/17 (17.6)
Yes	11/33 (33.3)
Target lesions	
<2	14/41 (34.2)
≥2	0/2 (0.0)
Number of Recurrences	
1	10/37 (27.0)
2	4/11 (36.4)
3	0/2 (0.0)
Days from Recurrence	
<21	7/26 (26.9)
≥21	7/24 (29.2)
Time Since Radiation	
3 to <6 months	9/18 (50.0)
≥6 months	5/32 (15.6)

KPS, Karnofsky performance score; LPS, Lansky performance score; n1, number of patients with a response; n2, number of patients in individual subgroups; ORR, objective response rate.

- While a greater proportion of patients had a response between 3 and 6 months from completion of RT, responses are likely genuine rather than pseudo-progression due to corroborating data suggesting presence of progressive disease (PD) prior to dordaviprone initiation.
    - Among 14 responders, 13 had at least one of the following lines of corroborating evidence: pathological confirmation of PD, increased perfusion imaging, restricted diffusion imaging, confirmation of PD on multiple MRIs, PD relative to both pre- and post-radiation MRIs, and/or incidence of new lesions

Conclusions

- RANO2.0 assessment of dordaviprone-treated patients suggests durable and clinically meaningful efficacy in recurrent H3K27M-mutant DMG.
- Four patients who had stable disease by RANO-HGG criteria were categorized as responders by RANO 2.0, and had associated improvements in multiple efficacy endpoints.
- Consistent with prior analysis by RANO-HGG/LGG criteria[14], responses were durable and associated with clinical benefit.
- The phase 3 ACTION trial (NCT05580562) is currently evaluating dordaviprone in H3 K27M-mutant diffuse glioma following standard front-line radiotherapy.

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Conflicts of Interest
TC has a consultancy/advisory role with Chimerix, Inc. and has stock ownership in Chimerix, Inc. JEA holds ONC201-related patents, is an employee of, and has stock ownership in Chimerix Inc. Jd and PYW have consultancy/advisory roles with Chimerix, Inc. ASM, SCR, and RST are employees of and has stock ownership in Chimerix, Inc. I-AR, MB, TTB, NB, AC, JJG, AMH, LBK, SCK, MES, NS, AS, and LT have no relevant disclosures.
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