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## Response by RANO 2.0 Criteria in ONC201 (Dordaviprone)-Treated Patients With Recurrent H3 K27M-Mutant Diffuse Midline Glioma

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### Objective

- To assess response to dordaviprone treatment per RANO 2.0 criteria in patients with recurrent H3 K27M-mutant diffuse midline glioma

### Conclusions

- RANO 2.0 assessment of dordaviprone-treated patients suggests durable and clinically meaningful efficacy in recurrent H3 K27M-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<sup>15</sup>, 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

**References:** 1. Sherock EB, et al. *Pediatr Blood Cancer*. 2007;49(3):306-12. 2. Solomon DA, et al. *Brain Pathol*. 2016;26(5):569-80. 3. Wang L, et al. *Hum Pathol*. 2016;79:89-96. 4. Cottom QT, et al. *Neuro Oncol*. 2022;24(Suppl 5):1-v45. 5. Khoury-Quang DA, et al. *Acta Neuropathol*. 2012;124(3):439-47. 6. Long W, et al. *Front Pharmacol*. 2017;8:495. 7. Cooney T, et al. *Neuro Oncol*. 2017;19(9):1279-80. 8. Erker C, et al. *Neuro Oncol*. 2022;24(1):141-52. 9. Allen JE, et al. *Sci Transl Med*. 2015;5(171):171ra17. 10. Free RB, et al. *Mol Pharmacol*. 2021;100(4):372-87. 11. Madhakar NS, et al. *Nat Commun*. 2019;10(1):5221. 12. Chazotte J, et al. *Cancer Cell*. 2019;55(7):723-737. 13. Groves PR, et al. *ACS Chem Biol*. 2019;14(5):1020-9. 14. MODEYSO, Package Insert. Jazz Pharmaceuticals, Inc.; 2025. 15. Arrillaga-Romany I, et al. *J Clin Oncol*. 2024;42(13):1542-52. 16. van den Bent MJ, et al. *Lancet Oncol*. 2011;12(6):583-93. 17. Wen PY, et al. *Neuro Oncol*. 2024;26(1):2-4.

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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 and up to 60% of adult DMG<sup>1–4</sup>
- 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<sup>5</sup>
- Currently, no systemic therapies have proven effective, and responses in the recurrent setting are rare<sup>6–8</sup>
  - 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).<sup>9–13</sup> It is the first and only FDA-approved treatment for recurrent H3 K27M-mutant DMG<sup>14</sup>

### 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)<sup>15</sup>
  - 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 (RANO) criteria
  - Because not all midline gliomas are uniformly enhancing, both RANO-HGG and RANO-LGG were used to quantitatively assess for both enhancing and nonenhancing lesions<sup>16</sup>
- Grade 3 treatment-related, treatment-emergent adverse events (TR-TEAEs) 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             |
| ORR, n (%) [95% CI] | 10 (20) [10–34]           | 13 (26) [15–40]      |
| BOR, n (%)          |                           |                      |
| CR                  | 1 (2)                     | 0                    |
| PR                  | 9 (18)                    | 6 (12)               |
| MR                  | 0                         | 7 (14)               |
| SD                  | 10 (20)                   | 8 (16)               |
| PD                  | 18 (36)                   | 14 (28)              |
| NE                  | 8 (16) <sup>a</sup>       | 11 (22) <sup>b</sup> |
| NA                  | 4 (8) <sup>c</sup>        | 4 (8) <sup>c</sup>   |
| DCR, n (%) [95% CI] | 20 (40) [26–55]           | 21 (42) [28–57]      |

<sup>a</sup>Five overall radiographic SD accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids.  
<sup>b</sup>Eight overall radiographic SD accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids.  
<sup>c</sup>Three patients did not have on-treatment monotherapy MRIs available for BICR; 1 patient censored prior to first on-treatment MRI.  
BICR, blind independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DMG, diffuse midline glioma; HGG, high-grade glioma; LGG, low-grade glioma; MR, minor response; MRI, magnetic resonance image; NA, not applicable; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease.

- 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)<sup>14</sup>
- 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)<sup>14</sup>

## 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)<sup>16</sup>
  - RANO 2.0 is a standard set of criteria recommended for all gliomas
  - Unified criteria provide assessment of tumors that are enhancing, nonenhancing, and both enhancing and nonenhancing
- This updated response evaluation was conducted to evaluate response by RANO 2.0 in the integrated analysis population

## Methods

- The study design, efficacy endpoints including response by RANO-HGG and RANO-LGG criteria, and safety have been previously reported<sup>14</sup>
- Select eligibility criteria included recurrent and/or progressive H3 K27M-mutant glioma (by NGS or IHC) and receipt of prior radiation therapy. Diffuse intrinsic pontine glioma, 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)

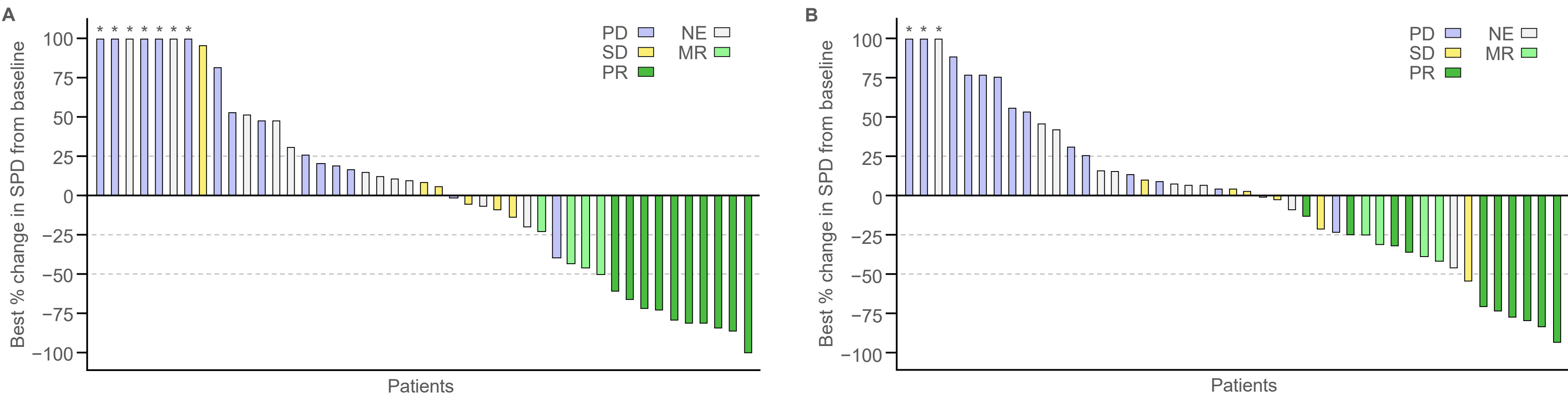
**Table 2. RANO 2.0 response criteria for tumors with enhancing and nonenhancing components<sup>17</sup>**

|                                                                                                                                                                                    | CR | PR | MR | SD | PD |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|----|----|----|
| <b>All the following:</b>                                                                                                                                                          |    |    |    |    |    |
| 1. Complete disappearance of all measurable enhancing and nonenhancing target lesions and all nonmeasurable and nontarget 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                                                                                                                                                   |    |    |    |    |    |
| <b>All the following:</b>                                                                                                                                                          |    |    |    |    |    |
| 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 nonmeasurable disease or nontarget lesions                                                                                                     |    |    |    |    |    |
| 4. Corticosteroid dose not greater than the dose at baseline scan                                                                                                                  |    |    |    |    |    |
| 5. Stable or improved clinically                                                                                                                                                   |    |    |    |    |    |
| Applies only to nonenhancing disease and can only be determined if the enhancing disease is at least stable. Requires <b>all</b> the following:                                    |    |    |    |    |    |
| 1. Decrease between 25%–50% in SPD or between 40%–65% of the total volume of nonenhancing 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 nonmeasurable disease or nontarget lesions                                                                                                                    |    |    |    |    |    |
| 4. Corticosteroid dose not greater than the dose at baseline scan                                                                                                                  |    |    |    |    |    |
| 5. Stable or improved clinically                                                                                                                                                   |    |    |    |    |    |

CR, complete response; FLAIR, fluid-attenuated inversion recovery; MR, minor response; MRI, magnetic resonance image; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; SPD, sum of products of perpendicular diameters.

## Results

**Figure 1. Waterfall plot of dordaviprone-treated patients with recurrent H3 K27M-mutant DMG with A) enhancing and B) nonenhancing tumor measurement by RANO 2.0 criteria**



\*Change >100%. Dotted lines indicate thresholds for PD (25% increase in sum of diameters of target lesions), MR (25% decrease in sum of diameters of target lesions), and PR (50% decrease in sum of diameters of target lesions). DMG, diffuse midline glioma; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; SPD, sum of products of perpendicular diameters.

**Table 3. Objective response assessment by RANO 2.0**

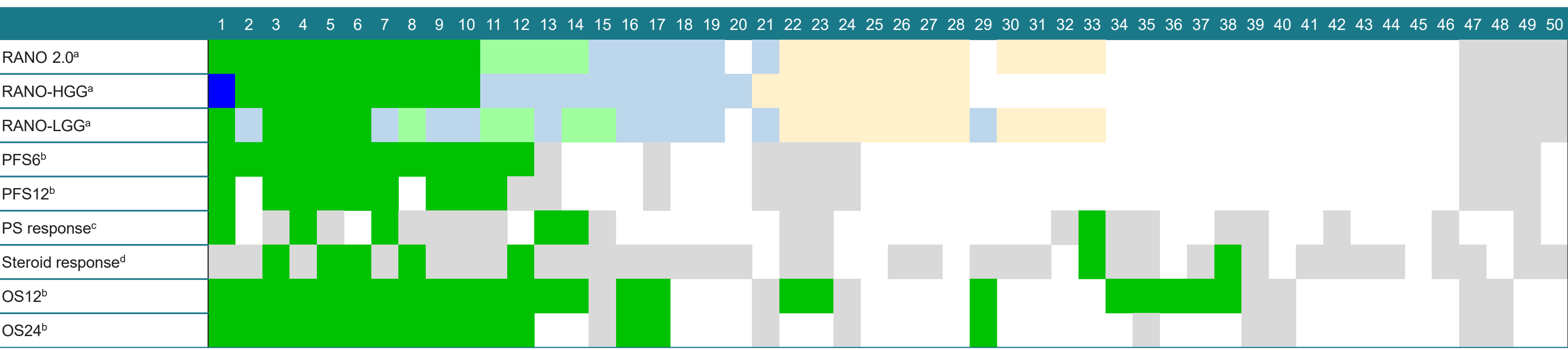
|                            | All Patients (N = 50) |
|----------------------------|-----------------------|
| ORR, n (%) [95% CI]        | 14 (28) [16–42]       |
| BOR, n (%)                 |                       |
| PR                         | 10 (20)               |
| MR                         | 4 (8)                 |
| SD                         | 6 (12) <sup>a</sup>   |
| PD                         | 15 (30)               |
| NE                         | 11 (22)               |
| NA <sup>b</sup>            | 4 (8)                 |
| Median TTR, months (range) | 4.6 (1.6–15.9)        |
| Median DOR, months (range) | 10.4 (7.4–15.4)       |
| DCR, n (%) [95% CI]        | 20 (40.0) [28–55]     |

<sup>a</sup>Includes one patient with unconfirmed response by RANO 2.0.

<sup>b</sup>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; DCR, disease control rate; DOR, duration of response; MR, minor response; MRI, magnetic resonance image; NA, not applicable; NE, not evaluable; ORR, objective response rate; 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)
  - 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%)
- RANO 2.0 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)

**Figure 2. Patient-level endpoints: objective response, progression-free survival, overall survival and corticosteroid and performance status responses**



|    | RANO <sup>a</sup> | PFS and OS <sup>b</sup> | PS Response <sup>c</sup> | Steroid Response <sup>d</sup> |
|----|-------------------|-------------------------|--------------------------|-------------------------------|
| CR | Yes               | Yes                     | Yes                      | Yes                           |
| PR | No                | No                      | No                       | No                            |
| MR | Censored          | Censored                | NE                       | NE                            |
| SD |                   |                         |                          |                               |
| NE |                   |                         |                          |                               |
| PD |                   |                         |                          |                               |
| NA |                   |                         |                          |                               |

<sup>a</sup>BOR by RANO criteria assessed by BICR. NE if PD with decreasing steroids or SD with increasing steroids. NA if no postbaseline assessments.

<sup>b</sup>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.

<sup>c</sup>Performance status response defined as increase in compared with baseline, while also having stable or reduced corticosteroid use. Increase must be confirmed at the next analysis time-point. Patients with baseline ≤80 were evaluable for this analysis.

<sup>d</sup>Steroid response defined as ≥50% reduction in average daily steroid dose compared with baseline or reduction ≥2 mg with stable or improved. Reduction must be confirmed at the next analysis time-point. Corticosteroids were converted into a dexamethasone equivalent dose. Patients receiving ≥4 mg 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) | ORR, n1/n2 (%)         | All Patients (N = 50) |
|---------------------|-----------------------|------------------------|-----------------------|
| Age                 |                       | Primary tumor location |                       |
| <18                 | 1/4 (25.0)            | Non-thalamus           | 3/17 (17.6)           |
| 18–<40              | 9/32 (28.1)           | Thalamus               | 11/33 (33.3)          |
| ≥40                 | 4/14 (28.6)           | Multifocal disease     |                       |
| Sex                 |                       | No                     | 3/17 (17.6)           |
| Female              | 8/23 (34.8)           | Yes                    | 11/33 (33.3)          |
| Male                | 6/27 (22.2)           | Target lesions         |                       |
| Race                |                       | <2                     | 14/41 (34.2)          |
| White               | 12/39 (30.8)          | ≥2                     | 0/2 (0.0)             |
| Other               | 2/11 (18.2)           | Number of recurrences  |                       |
| Ethnicity           |                       | 1                      | 10/37 (27.0)          |
| Hispanic/Latino     | 1/4 (25.0)            | 2                      | 4/11 (36.4)           |
| Not Hispanic/Latino | 11/41 (26.8)          | 3                      | 0/2 (0.0)             |
| Unknown             | 2/5 (40.0)            | Days from recurrence   |                       |
| KPS/LPS             |                       | <21                    | 7/26 (26.9)           |
| 60–70               | 1/14 (7.1)            | ≥21                    | 7/24 (29.2)           |
| 80                  | 8/20 (34.8)           | Time since radiation   |                       |
| 90–100              | 5/16 (31.3)           | 3 to <6 months         | 9/18 (50.0)           |
| Tumor Size          |                       | ≥6 months              | 5/32 (15.6)           |
| <10 cm <sup>2</sup> | 6/22 (27.3)           |                        |                       |
| ≥10 cm <sup>2</sup> | 8/27 (29.6)           |                        |                       |
| Unknown             | 0/1 (0.0)             |                        |                       |

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; RANO, Response Assessment in Neuro-Oncology.

- Responses occurred at a higher rate among patients with a higher performance score and fewer target lesions (Table 4)

- While a greater proportion of patients had a response between 3 and 6 months from completion of radiation, 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, restricted diffusion, confirmation of PD on multiple MRIs, PD relative to both pre and postradiation MRIs, and/or incidence of new lesions