RTID-01

ONC201-108: A Randomized Phase 3 Study of ONC201 in Patients with Newly Diagnosed H3 K27M-mutant Diffuse Glioma

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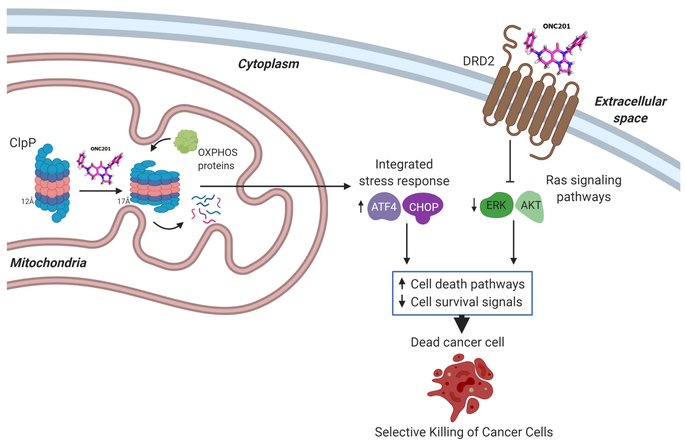
Introduction

- 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, with a median overall survival of 0.73 years, compared to 4.59 years in patients with H3 K27M wild-type tumors.[4]
  - In 2016, the World Health Organization classified H3 K27M-mutant DMG as a distinct form of Grade IV glioma, regardless of histological features.[5]
- 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 (**Figure 1**).[6-10]

Figure 1. ONC201 Mechanism of Action



AKT, protein kinase B; ATF4, activating transcription factor 4; CHOP, C/EBP-homologous protein; ClpP, caseinolytic protease P; DRD2, dopamine receptor D2; ERK, extracellular-regulated kinase. Originally published in Anderson, et al. *Clin Cancer Res*. 2022;28:1773–82.

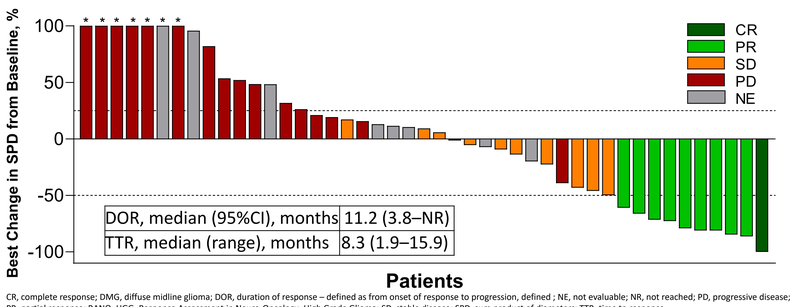
- An integrated analysis of 50 adult and pediatric with recurrent H3 K27M-mutant DMG who received ONC201 monotherapy in one of five open-label studies was previously conducted (**Table 1** & **Figure 2**).[11]

Table 1. ONC201 ORR in Patients with Recurrent H3 K27M DMG

	Total Population (N=50)		
	RANO-HGG[1]	RANO-LGG[2]	Combined HGG/LGG[3]
ORR, n (%) [95%CI]	**10 (20) [10–34]**	**13 (26) [15–40]**	**15 (30) [18–45]**
CR	1 (2)	0 (0)	1 (2)
PR	9 (18)	6 (12)	9 (18)
MR	NA	7 (14)	5 (10)
SD	10 (20)	8 (16)	7 (14)
NE	8 (16)[4]	11 (22)[5]	11 (22)[5]
PD	18 (36)	14 (28)	13 (26)
NA	4 (8)[6]	4 (8)[6]	4 (8)[6]
DCR, 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 SD accompanied by increase in corticosteroids; three overall radiographic PD accompanied by decrease in corticosteroids; [5]Eight overall radiographic SD accompanied by increase in corticosteroids; three overall radiographic PD 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; CR, complete response; DCR, disease control rate (CR + PR + SD); HGG, high grade glioma; LGG, low grade glioma; MR, minor response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RANO, response assessment in neuro-oncology; SD, stable disease.

Figure 2. Waterfall Plot of ONC201-treated Patients with recurrent H3 K27M-mutant DMG (RANO-HGG)



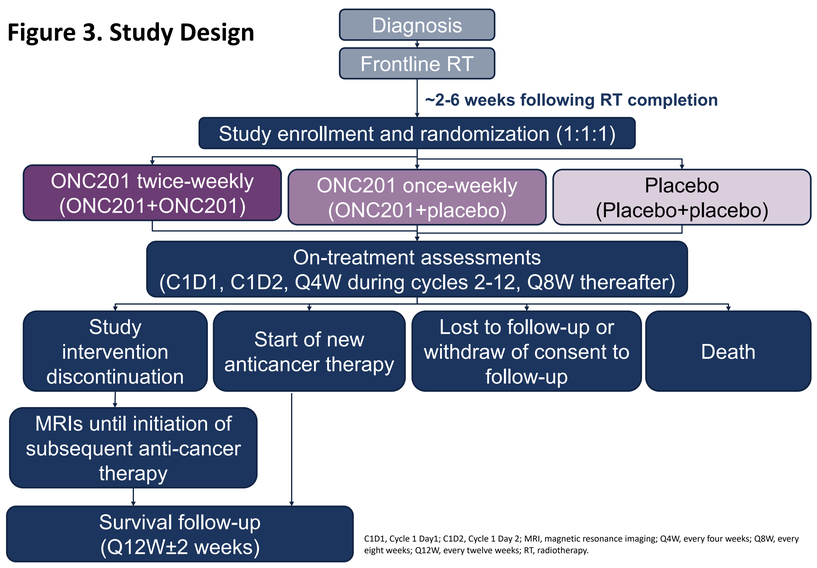
CR, complete response; DMG, diffuse midline glioma; DOR, duration of response – defined as from onset of response to progression, defined ; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; RANO–HGG, Response Assessment in Neuro-Oncology–High Grade Glioma; SD, stable 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)[11]
- **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)[11]

Methods

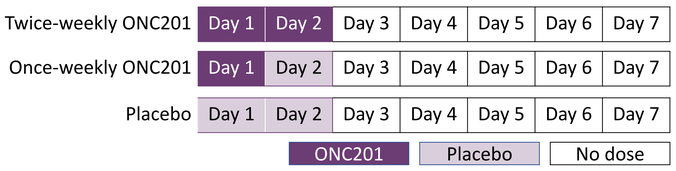
- The ACTION trial (ONC201-108) will be a randomized, double-blind, placebo-controlled, parallel-group international phase 3 trial of patients with newly diagnosed, H3 K27M-confirmed DMG previously treated with radiation (**Figure 3**).
- Randomization will be 1:1:1 to once-weekly ONC201, twice-weekly ONC201 on consecutive days, or placebo (**Figure 4**).
  - Dose will be scaled by body weight in patients ≤52.5 kg.
  - Dose may be dissolved in Gatorade/Powerade for those unable to swallow capsules.

Figure 3. Study Design



C1D1, Cycle 1 Day1; C1D2, Cycle 1 Day 2; MRI, magnetic resonance imaging; Q4W, every four weeks; Q8W, every eight weeks; Q12W, every twelve weeks; RT, radiotherapy.

Figure 4. Treatment Arms



- Dose modification: Grade 3/4 treatment-related treatment-emergent adverse event does not adequately resolve with medical management.
- Treatment discontinuation: dependent on individual response, disease progression, and tolerability. Treatment beyond first progression at investigator's discretion; concomitant treatment with bevacizumab and/or reirradiation permitted.
- Eligibility criteria (**Table 2**) is not restricted by age (if ≥10 kg).

Table 2. Select Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
H3 K27M-mutant diffuse glioma	Spinal tumor or DIPG
Body weight ≥10 kg	Leptomeningeal spread or CSF dissemination
Randomize <6 weeks from RT (54-60 Gy)	Concurrent malignancy
Baseline MRI 2-6 weeks after RT	New lesion(s) outside the radiation field
KPS/LPS ≥70	QTc> 480 msec
Stable or decreasing dose of corticosteroids and anti-seizure medications for seven days	Laboratory test results not meeting established parameters
Sufficient washout from: • Temozolomide (3 weeks) • DRD2 antagonists (2 weeks) • Investigational agent (4 weeks) • Strong CYP3A4/5 inhibitors (3 days) • Strong CYP3A4/5 inducers (2 weeks)	Prior receipt of the following at any time: • Whole-brain radiotherapy • Proton therapy • ONC201 • ONC206 • Bevacizumab • Tumor-treating fields

DIPG, diffuse intrinsic pontine glioma; DRD2, dopamine receptor D2; KPS, Karnofsky performance score; LPS, Lansky Performance Score; MRI, magnetic resonance imaging; QTc, corrected heart rate.

- Cycles length: 28 days, visits every four weeks through Cycle 12 and every eight weeks thereafter (**Table 3**).
  - Additional MRIs: prior to radiotherapy (if available) and 2-6 weeks post radiation, prior to randomization.

Table 3. Study Visit Summary

	C1D1	C1D2	C2D1	C3-12 (Q4W)	C≥13 (Q8W)
Weight & height	✓		✓	✓	✓
Physical exam & vitals	✓			C3D1 + Q8W	
12-lead ECG	✓	✓		C3D1 + Q8W	
QoL	✓			C3D1 + Q8W	
KPS/LPS	✓			C3D1 + Q8W	
NANO	✓	✓		C3D1 + Q8W	
MRI				C3D1 + Q8W	
Blood Collection					
Hematology	✓		✓	✓	✓
Serum chemistry	✓		✓	✓	✓
Biomarker	✓			C3D1 + Q8W	
Plasma PK	✓	✓		C3D1 + Q8W	

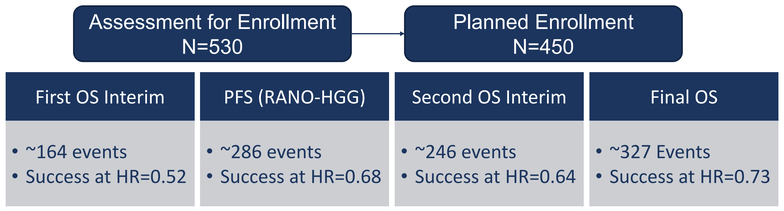
C, cycle; D, day; ECG, electrocardiogram; KPS, Karnofsky performance score; LPS, Lansky Performance Score; MRI, magnetic resonance imaging; NANO, neurological assessment in neuro-oncology; PK, pharmacokinetics; Q4W, every four weeks; Q8W, every eight weeks.

Table 4. Objectives and Endpoints

Objective	Endpoint
Primary	
Efficacy	• OS • PFS (RANO-HGG)
Secondary	
Safety	• AE incidence (NCI-CTCAE v5.0) • Change from baseline and distribution
Efficacy	• PFS in patients with measurable contrast-enhancing disease
Clinical Benefit	• Corticosteroid response • Performance status response
Quality of Life	• Change from baseline in: • EORTC-QLQ-C30, QLQ-BN20, MDASI-BT, and NANO (Age >18 years) • PedsQL (Age ≤18 years)
Exploratory	
Pharmacokinetics	• Plasma concentration and pharmacokinetic parameters
Exposure-response	• Correlation of exposure and efficacy/safety parameters
Efficacy	• PFS (RANO-LGG)
Biomarkers	• Correlation of molecular profile and efficacy parameters
HCRU	• HCRU

AE, adverse event; EORTC-QLQ-BN20, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Brain Module; EORTC-QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life-Core Questionnaire; HCRU, healthcare resource utilization; HGG, high-grade glioma; LGG, low-grade glioma; MDASI-BT, MD Anderson Symptom Inventory Brain Tumor Module; NANO, neurological assessment in neuro-oncology; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PedsQL, Pediatric Quality of Life Inventory; PFS, progression-free survival; RANO, response assessment in neuro-oncology.

Figure 5. Population Size and Statistical Analyses



HR, hazard ratio; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; RANO-HGG, response assessment in neuro-oncology – high-grade glioma.

- End of study is defined as when all patients have discontinued, are lost to follow-up, have withdrawn consent, died, or when the sponsor decides to terminate the study.
- Enrollment will begin in late 2022, with additional sites opening early 2023.

References

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Disclosures

AL, IA-R, and **SM** have no relevant disclosures; **AM, DY, JA**, and **RT** are employees of and have stock ownership in Chimerix, Inc; **MvdB** and **PW** have served as consultants for Chimerix, Inc; **SLM** served on an advisory board for Chimerix, Inc. **TC** has received research funding from, has stock ownership in, and has served as a paid consultant for Chimerix, Inc.

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Poster PDF

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