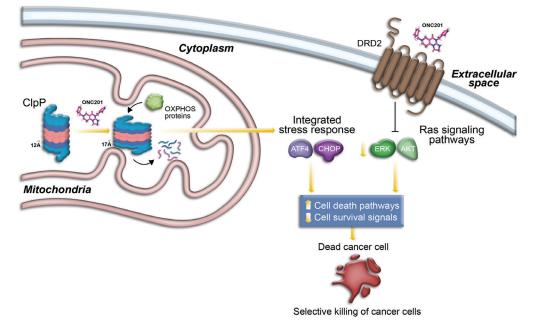
Single Agent Activity of ONC201 in Non-midline H3 K27M-Mutant Diffuse Gliomas

¹Miami Cancer Institute, Miami, FL, USA; ²Levine Cancer Institute, Charlotte, NC, USA; ⁴Columbia University Irving Medical Center New York City, NY, USA; ⁵Massachusetts General Hospital, Boston, MA, USA; ⁶New York University School of Medicine, New York City, NY, USA; ⁷Oncoceutics Inc, Philadelphia, PA, USA; ⁸Chimerix, Inc, Durham, NC, USA; ⁹Dana-Farber Brigham and Women's Cancer Center, Boston, MA, USA

Background

- Histone H3 K27M-mutant gliomas are associated with a poor prognosis and disproportionately affect children and young adults¹
- Radiotherapy is the sole standard-of-care, as the anatomic location of the tumor may severely limit surgical resection¹
- ONC201, an investigational anticancer small molecule, is a dopamine receptor D2/3 antagonist and a caseinolytic protease P agonist that has induced durable tumor regressions by response assessment for neuro-oncology high grade glioma (RANO-HGG) criteria in a registration cohort of patients with recurrent H3 K27Mmutant diffuse midline glioma treated with single agent ONC201²
- While the H3 K27M mutation is associated with poor prognosis in diffuse midline gliomas, its prognostic significance for non-midline gliomas remains uncertain^{3,4}

Figure 1. ONC201 Mechanism of Action^{2,5-7}



AKT = protein kinase B; ATF4 = activating transcription factor 4; CHOP = C/EBP-homologous protein; ClpP = caseinolytic protease P; DLT = dose-limiting toxicity; DRD2 = dopamine receptor D2; ERK = extracellular-regulated kinase; OXPHOS = oxidative phosphorylation.

Objective

• To evaluate clinical efficacy of ONC201 in H3 K27M-mutant diffuse gliomas with involvement of non-midline CNS structures

Methods

Patients

- Pediatric and adult patients (≥2 years of age) with recurrent H3 K27M-mutant diffuse glioma enrolled in ONC201 studies but excluded from the registration cohort because of involvement of non-midline CNS structures
- ONC006 (NCT02525692)
- ONC013 (NCT03295396)
- ONC014 (NCT03416530; pediatric study)
- ONC018 (NCT03134131; expanded access program)
- ONC016 (compassionate use program)
- Karnofsky Performance Status (KPS) ≥60

Tumor characteristics

- Non-midline H3 K27M-mutant diffuse glioma
- Measurable (≥1 cm in tumor diameter) contrast-enhancing disease by RANO-HGG criteria with each measurement
- Non–contrast-enhancing tumors, diffuse intrinsic pontine glioma, and spinal tumors were excluded

Treatment

- Oral ONC201 monotherapy (oral; 625 mg once weekly [scaled by body weight for pediatric patients])
- Adequate washout >90 days from prior radiation; adequate washout from prior anticancer therapy

Assessments

- The primary endpoint was objective response rate (ORR) by **RANO-HGG** criteria
- Secondary endpoints included ORR by RANO-low grade glioma (RAN-LGG) criteria, duration of response, and performance status response rate

Results

• Five patients with non-midline H3 K27M-mutant diffuse gliomas were included in this analysis

Table. Patients With Non-midline H3 K27M-Mutant **Diffuse Gliomas: Demographics and Baseline Characteristics**

Characteristic Age, y, median (range) Female sex, n (%) Race, n (%) White Black Asian

Weight, kg, median (range)

KPS score, median (range)

Primary tumor location, n (%) Frontal lobe Temporal lobe Parietal lobe

Multifocal disease, n (%) Yes No

H3 K27M mutation detection, n Immunohistochemistry Next generation sequencing

Number of recurrences, median

Time from prior radiation, wk, me

Dexamethasone dose, mg, med

Re-irradiation, n (%)

*Patient had tumor with H3.1 K27 mutation KPS = Karnofsky performance status.

- No serious adverse events were reported

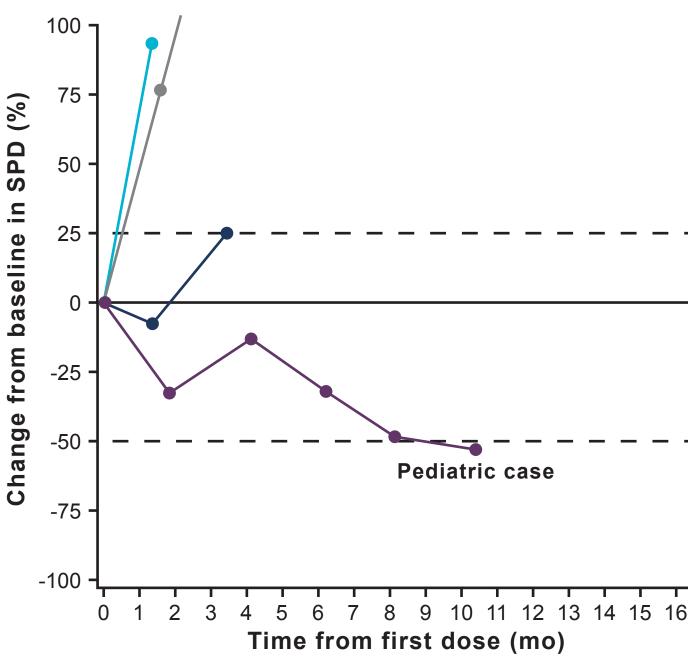
Poster: CTNI-27

Yazmin Odia, MD, MS, FAAN¹; Ashley Sumrall, MD, FACP²; Timothy Cloughesy, MD³; Matthew Hall, MD, MBA¹; Doured Daghistani, MD¹; Minesh Mehta, MD¹; Andrew Lassman, MD⁴; Isabel Arrillaga-Romany, MD, PhD⁵; Sharon Gardner, MD, PhD⁶; Rohinton Tarapore, PhD^{7,8}; Guangrong Lu, MBBS⁷; Joshua Allen, PhD^{7,8}; Patrick Wen, MD, PhD⁹

	Patients (N=5)					
	33 (13-38)					
	4 (80.0)					
	3 (60.0) 1 (20.0) 1 (20.0)					
	59.6 (54-101.9)					
	90 (70-100)					
	3 (60.0) 1 (20.0) 1 (20.0)					
	3 (60.0) 2 (40.0)					
(%)	4 (80.0) 1 (20.0)*					
(range)	1 (1-1)					
edian (range)	27.9 (23.3-68)					
lian (range)	0 (0-24)					
	2 (40.0)					

• No dose modifications or dose-limiting toxicities were observed

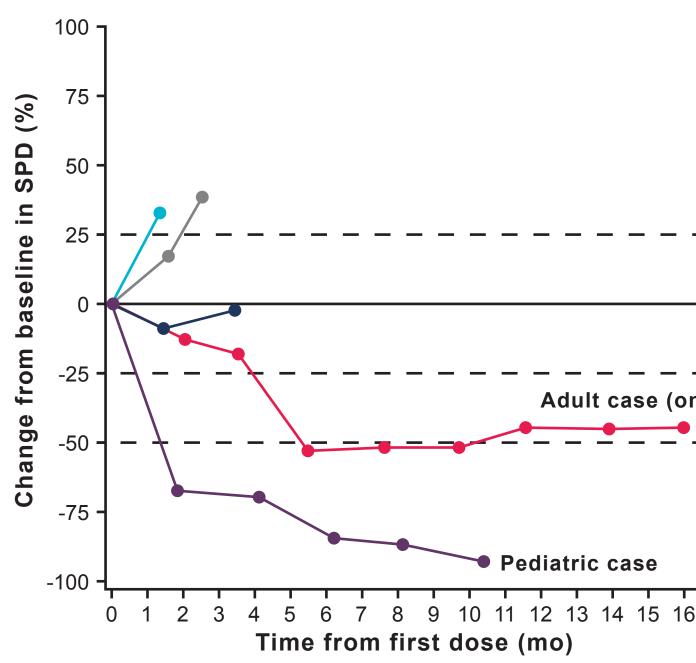
Figure 2. Patients With Non-Midline H3 K27M-Mu **Diffuse Gliomas: Change in Tumor Measuremen** Time (RANO-HGG)*



Enrollment cut-off: Feb 26, 2020; data cut-off: May 31, 2021 *Only patients with measurable target enhancing lesions at both baseline and post-baseline ass

were included BICR = Blinded Independent Central Review; RANO-HGG = response assessment for neuro-on grade glioma; SPD = sum of products of perpendicular diameters (target enhancing lesions per l

Figure 3. Patients With Non-Midline H3 K27M-Mu Diffuse Gliomas: Change in Tumor Measuremen Time (RANO-LGG)*



Enrollment cut-off: Feb 26, 2020; data cut-off: May 31, 2021. *Only patients with measurable target non-enhancing lesions at both baseline and post-baseline assessments

BICR = Blinded Independent Central Review; RANO-LGG = response assessment for neuro-oncology low grade glioma; SPD = sum of products of perpendicular diameters (target non-enhancing lesions per BICR).

The Society for NeuroOncology (SNO) 2021 • November 18–21, 2021 • Boston, MA

 Molecular features: MGMT promoter unmethylated, TP53 a ATRX loss, PIK3CA mutation Prior treatment CCRT: Jul 2018 – Aug 2018 TTFields therapy: Sep 2018 – Aug 2019 ONC201: Dec 2019 – Present PR: May 2020 (5.5 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 months Steroid usage (1 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Molecular features: MGMT promoter unmethylated, TP53 a ATRX mutation Molecular features: MGMT promoter unmethylated, TP53 a ATRX mutation Molecular features: MGMT promoter unmethylated, TP53 a ATRX mutation Prior treatment CCRT: Jul 2019 – Aug 2019 TMZ: Oct 2019 – Jan 2020 ONC201: Feb 2020 – Apr 2021 Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mor Mumber Baseline 0 morths 7.1 metag 0 mg maximum (mmetageme	Figure 4.	Adult Ca	se Stuc	ły				Pediatric				
ATRX loss. PIK3CA mutation Prior treatment CCRF. Jul 2018 – Aug 2018 TTE-lields therapy: Sep 2018 – Aug 2019 ONC201: Dec 2019 – Present PR: May 2019; Sep 2018 – Aug 2019 ONC201: Dec 2019 – Present PR: May 2019 (5.5 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months The stable throughout Dec 2019 – Jonet 1.1 and 1.2 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 mort Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.2 mort Steroid usage (0 mg) and KPS were stable th						 Integrated diagnosis: frontal glioma, H3 K27M mutation (Jun 20 						
 Prior treatment CRT: Jul 2018 – Aug 2018 TTT: Fields therapy: Sep 2018 – Aug 2019 CRT: Aug 2019 – Present PR: May 2020 (3.5 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 months Steroid usage (0 mg) and KPS were stable throughout Baseline 1.9 months 5.8 months 10.3 months Monther 1.9 months 5.8 months 10.3 months Monther 1.9 months 5.8 months 10.3 months 10.3 months 10.3 months 10.3 months 10.3 months 10.3 months 10.4 monther 1.9 months 5.8 months 10.3 months 10.4 monther 1.9 months 1			-		nmethylate	d, IDH wildtype,			//GIVIT pi	omoter u	nmethylated	u, 1955 and
TMZ: Aug 2018 TTFields thrapy: Sep 2018 – Aug 2019 NC201: Dec 2019 – Present PR: May 2020 (5.5 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months The stable difference of the stable differe			natation				 Prior trea 	tment				
 TTR: dd thag 2020 TR: Sep 2020 Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Steroid usage (0 mg) and KPS were stable throughout Baseline Miniber Baseline 	– CCRT:	Jul 2018 – /	Aug 2018	3			 Surgery 	/: May 2019); Jun 20	19		
 ONC201: Feb 2020 – Apr 2021 Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Imperson 1 and the stable of throughout Baseline 5.5 months 9.6 months Imperson 1 and the stable of throughout Baseline 5.5 months 9.6 months Imperson 1 and the stable of throughout Baseline 5.5 months 9.6 months Imperson 1 and the stable of throughout Imperson 1 and the stable of throughout 1 and through the stable of through	– TMZ: A	ug 2018					– CCRT:	Jul 2019 – /	Aug 2019	9		
 PR: May 2020 (5.5 months) CR: Sep 2020 (9.6 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Seroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months March 19, 19, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10	– TTField	Is therapy: S	Sep 2018	3 – Aug 2	019							
 CR: Sep 2020 (9.6 months) Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months Image: Stable difference of the stable difference o				t							able throug	ubout
 Steroid usage (0 mg) and KPS were stable throughout Baseline 5.5 months 9.6 months S.5 months 9.6 months S.5 months 9.6 months S.5 months 9.6 months Seeson 0 100 100 100 100 100 100 100 100 100	•	•									•	
Baseline5.5 months9.6 monthsImage: Source of the second of the		Υ.		S were st	able throug	ahout	Baselli	le 1.91	nonths	5.6 11	iontins	
Assessor Baseline measurable (cm ²) Number (sc ^m) Dashed (sc ^m) In TL area (%, RANO- lisease Best real (cm ²) Assessor enhancing measurable (sc ^m) Number (sc ^m) In tL area (%, RANO- lisease Best real (sc ^m) PR (RANU PR (RA		• • • • • •			-	-	13-2					Ca
Assessor enhancing measurable (cm²) Int_area (m²) Best reaponse (cm²) Assessor enhancing measurable (cm²) Investigator Yes 1 14.88 -52.6 SD (RANC PR (RANC) PR (RANC PR (RANC P							A. 2		1	PA		
Assessor enhancing measurable (crite) Number (crite) Daspinable (crite) in TL area (crite) Best real (crite) Assessor enhancing measurable Number (crite) <				AND D						-		
Assessor enhancing measurable (cm²) Number (srisease) Dashing (srisease) in TL area (srisease) Best real (cm²) Investigator Yes 1 14.88 -52.6 SD (RANG PR (RANG PR (RANG PR (RANG PR (RANG PR (RANG PR (RANG PR (RANG PR (RANG)) Assessor Baseline onhancing measurable (srisease) Number (srisease) Investigator Yes 1 14.88 -52.6 SD (RANG PR (RANG PR (RANG PR (RANG PR (RANG)) Assessor Baseline onhancing measurable (srisease) Number (srisease) Investigator Yes 1 14.88 -52.6 SD (RANG PR (RANG PR (RANG PR (RANG PR (RANG)) Assessor Baseline onhancing measurable (srisease) Number (srisease) Investigator Yes 1 14.88 -52.6 SD (RANG PR (RANG PR (RANG)) Assessor Investigator Na Na Best response (criteria) Best response (criteria) So (RANG) So (RANG) So (RANG) So (RANG) Co (So (So (So (So (So (So (So (So (So (S				14			De la	\$5			3	調査
Assessor enhancing measurable (cm²) Number (srite (cm²) Destree (srite (cm²) Best real (cm²) Best response (srite (cm²) Assessor Easeline enhancing (cm²) Investigator Yes 1 14.88 -52.6 SD (RANC PR (R	R		R	THE I				Baseline			Best change	
Important of the second difference on th	5105	1-3	E C	No.			Assessor	enhancing			in TL area	Best respo
BICR Yes 1 14.88 -52.6 SD (RANG PR (RAMG) BICR Yes 1 14.88 -52.6 SD (RANG PR (RAMG) Assessor Easeline measurable disease Number of TL disease Bisseline TL area (cm ²) Best response (%, RANO- HGG) The of the five patients showed objective responses by RANG HGG criteria (ORR, 40%) as assessed by the investigator b were not confirmed by blinded independent central review (fit a response by RANO-LGG by the BICR, resulting in RA LGG ORR of 40% No 0 NA NA (RANO-HGG) PR (RANO-HGG) Patients with noted RANO-LGG responses were on-treat for 14 and 23 months NRCR = blinded independent central review; CCRT = concurrent demoradiotherapy (with TMZ); CR = complete sponse; IDH = locitrat dehydrogenaes; MGMT = 0(9)-methylagnane ONA methylamsterase; NA = nd policible; RP = patient response; RANO-LGG No dose modifications or dose-limiting toxicities were obset		25	14	ET S		RYE J				(cm²)	-	
BICR Yes 1 14.88 -52.6 PR (RAM) Massessor Baseline enhancing measurable disease Number Baseline TL area (cm ²) Best change in TL area (cm ²) Best response (criteria) Best response (criteria) Investigator Yes 1 1.44 100 CR (RANO-HGG) - However, the two responding patients were deemed to M a response by RANO-LGG by the BICR, resulting in RA LGG ORR of 40% BICR No 0 NA NA (RANO-HGG) PR (RANO-LGG) BICR No 0 NA NA (RANO-HGG) PR (RANO-LGG) BICR No 0 NA NA (RANO-LGG) PR (RANO-LGG) BICR No 0 NA NA (RANO-LGG) PR (RANO-LGG)							Investigator	Yes	2	11.90	-87	PR (RANO-H
Assessor Baseline enhancing measurable disease Number of TL area (cm ²) Best change in TL area (cm ²) Best change in TL area (cm ²) Best change in TL area (cm ²) Best response (criteria) Investigator Yes 1 1.44 100 CR (RANO-HGG) (CR (RANO-HGG)) BICR No 0 NA NA (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) BICR No 0 NA NA (RANO-HGG) PR (RANO-HGG) BICR No 0 NA NA (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) DR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) DR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) DR (RANO-HGG) PR (RANO-HGG) PR (RANO-HGG) PR (RA				- co				Vee	4	44.00	50.0	SD (RANO-H
Assessor Baseline enhancing measurable disease Number of TL Baseline of TL Best change in TL area (m?) Best change in TL area (%, RANO- HGG) Best response (%, RANO- HGG) Best response (criteria) • Two of the five patients showed objective responses by RAN HGG criteria (ORR, 40%) as assessed by the investigator b were not confirmed by blinded independent central review (I - However, the two responding patients were deemed to the a response by RANO-LGG by the BICR, resulting in RA LGG ORR of 40% BICR No 0 NA NA (RANO-HGG) PR (RANO-LGG) BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; IDH = isocitate dehydrogenase; RAM-HGG = neuro-oncology hg grade glioma; RANO-LGG = neuro-oncology hg grade in the sponse by RANO-LGG = neuro-oncology hg grade glioma; RANO-HGG) PR (RANO-HGG) BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; RANO-HGG = neuro-oncology hg grade glioma; RANO-LGG = neuro-oncology hg grade gliom	A CONTRACTOR			O			DICK	165	1	14.00	-52.0	PR (RANO-I
Investigator Yes 1 1.44 100 CR (RANO-HGG) BICR No 0 NA NA NA (RANO-HGG) Patients with noted RANO-LGG responses were on-treat for 14 and 23 months BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; NA = not applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro- NA (RANO-LGG = neuro- Na (RANO-HGG)	R	enhancing measurable		TL area	in TL area (%, RANO-	Best response	 response; RANO-H TL = target lesion; Concl Two of th HGG crite were not Howey 	IGG = neuro-oncolo TMZ = temozolomic e five patier eria (ORR, 4 confirmed b /er, the two	nts show 40%) as y blinde respond	ed objecti assessed d indepen	Ve response by the inve dent centra	es by RAN stigator built review (Bl emed to ha
BICR No 0 NA NA NA (RANO-HGG) PR (RANO-LGG) BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; NA = not applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro- NA (RANO-HGG) - Patients with noted RANO-LGG responses were on-treat for 14 and 23 months BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro- - Responses were associated with clinical benefit of increations or dose-limiting toxicities were obset	Investigator		1	1.44		CR (RANO-HGG)	•				·	0
BICR No 0 NA NA PR (RANO-LGG) BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete esponse; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; NA = not applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro- PR (RANO-LGG) – Responses were associated with clinical benefit of increase No 0 NA NA PR (RANO-LGG) – Responses were associated with clinical benefit of increase BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete esponse; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; NA = not applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro- – No dose modifications or dose-limiting toxicities were observed	O the second sec									-LGG res	oonses were	e on-treatm
BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); CR = complete response; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; NA = not applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro-	BICR	No	0	NA	NA					ed with cl	inical benef	it of increas
applicable; PR = partial response; RANO-HGG = neuro-oncology high grade glioma; RANO-LGG = neuro-		-				· · · · ·	mobilit	y and level	of alertn	ess		
• No serious adverse events were reported	applicable; PR = p	partial response; RA	NO-HGG = ne	euro-oncology h	nigh grade glioma;	RANO-LGG = neuro-						vere observ
		e giloma, TE – targe				- temozoiomide.	 No serior 	us adverse	events w	ere repo	rted	
	oncology low grad											

Editorial assistance was provided by Synchrony Medical Communications, LLC, West Chester, PA, USA, and funded by Chimerix, Inc, Durham, NC, USA.