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

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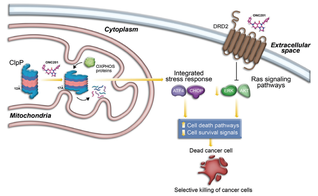
Background

- Histone H3 K27M-mutant gliomas are associated with a poor prognosis and disproportionately affect children and young adults[1]
- Radiotherapy is the sole standard-of-care, as the anatomic location of the tumor may severely limit surgical resection[1]
- 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 K27M-mutant diffuse midline glioma treated with single agent ONC201[2]
- 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

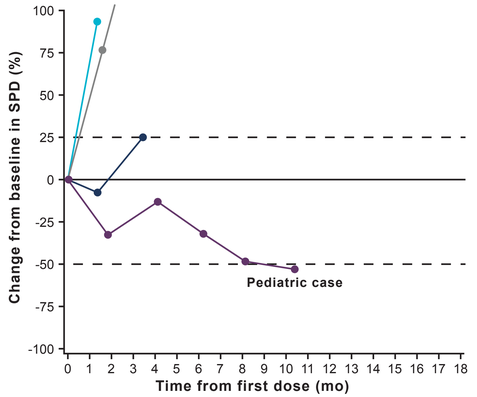
Table. Patients With Non-midline H3 K27M-Mutant Diffuse Gliomas: Demographics and Baseline Characteristics

Characteristic	Patients (N=5)
Age, y, median (range)	33 (13-38)
Female sex, n (%)	4 (80.0)
Race, n (%)	
White	3 (60.0)
Black	1 (20.0)
Asian	1 (20.0)
Weight, kg, median (range)	59.6 (54-101.9)
KPS score, median (range)	90 (70-100)
Primary tumor location, n (%)	
Frontal lobe	3 (60.0)
Temporal lobe	1 (20.0)
Parietal lobe	1 (20.0)
Multifocal disease, n (%)	
Yes	3 (60.0)
No	2 (40.0)
H3 K27M mutation detection, n (%)	
Immunohistochemistry	4 (80.0)
Next generation sequencing	1 (20.0)*
Number of recurrences, median (range)	1 (1-1)
Time from prior radiation, wk, median (range)	27.9 (23.3-68)
Dexamethasone dose, mg, median (range)	0 (0-24)
Re-irradiation, n (%)	2 (40.0)

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

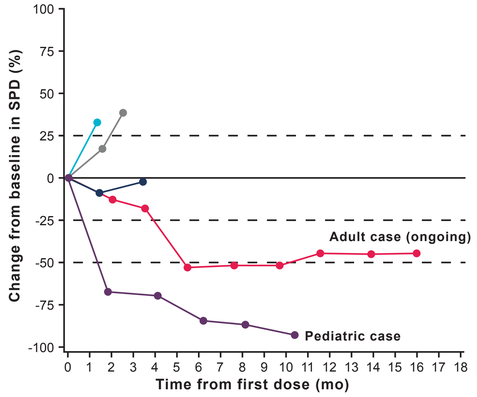
- No dose modifications or dose-limiting toxicities were observed
- No serious adverse events were reported

Figure 2. Patients With Non-Midline H3 K27M-Mutant Diffuse Gliomas: Change in Tumor Measurement Over 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 assessments were included.
BICR = Blinded Independent Central Review; RANO-HGG = response assessment for neuro-oncology high grade glioma; SPD = sum of products of perpendicular diameters (target enhancing lesions per BICR).

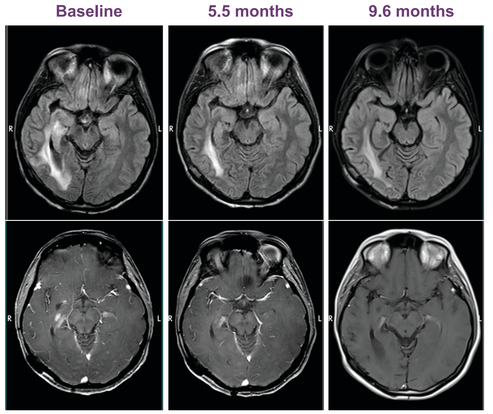
Figure 3. Patients With Non-Midline H3 K27M-Mutant Diffuse Gliomas: Change in Tumor Measurement Over Time (RANO-LGG)*



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 were included.
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).

Figure 4. Adult Case Study

- Integrated diagnosis: frontal glioma, H3 K27M mutation (Jun 2018)
- Molecular features: MGMT promoter unmethylated, IDH wildtype, ATRX loss, PIK3CA mutation
- Prior treatment
  - CCRT: Jul 2018 – Aug 2018
  - TMZ: Aug 2018
  - TTFields therapy: Sep 2018 – Aug 2019
- ONC201: Dec 2019 – Present
- PR: May 2020 (5.5 months)
- CR: Sep 2020 (9.6 months)
- Steroid usage (0 mg) and KPS were stable throughout

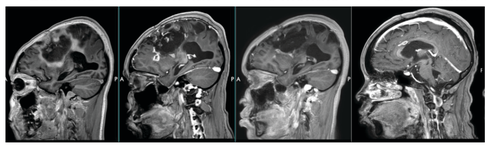


Assessor	Baseline enhancing measurable disease	Number of TL	Baseline TL area (cm^2)	Best change in TL area (%, RANO-HGG)	Best response (criteria)
Investigator	Yes	1	1.44	100	CR (RANO-HGG)
BICR	No	0	NA	NA	NA (RANO-HGG) PR (RANO-LGG)

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-oncology low grade glioma; TL = target lesion; TTFields = tumor treating fields; TMZ = temozolomide.

Figure 5. Pediatric Case Study

- Integrated diagnosis: frontal glioma, H3 K27M mutation (Jun 2018)
- Molecular features: MGMT promoter unmethylated, TP53 and ATRX mutation
- Prior treatment
  - Surgery: May 2019; Jun 2019
  - CCRT: Jul 2019 – Aug 2019
  - TMZ: Oct 2019 – Jan 2020
- ONC201: Feb 2020 – Apr 2021
- Steroid usage (0 mg) and KPS were stable throughout



Assessor	Baseline enhancing measurable disease	Number of TL	Baseline TL area (cm^2)	Best change in TL area (%, RANO-HGG)	Best response (criteria)
Investigator	Yes	2	11.90	-87	PR (RANO-HGG)
BICR	Yes	1	14.88	-52.6	SD (RANO-HGG) PR (RANO-LGG)

BICR = blinded independent central review; CCRT = concurrent chemoradiotherapy (with TMZ); 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-oncology low grade glioma; TL = target lesion; TMZ = temozolomide.

Conclusions

- Two of the five patients showed objective responses by RANO-HGG criteria (ORR, 40%) as assessed by the investigator but were not confirmed by blinded independent central review (BICR)
  - However, the two responding patients were deemed to have a response by RANO-LGG by the BICR, resulting in RANO-LGG ORR of 40%
  - Patients with noted RANO-LGG responses were on-treatment for 14 and 23 months
  - Responses were associated with clinical benefit of increased mobility and level of alertness
- No dose modifications or dose-limiting toxicities were observed
- No serious adverse events were reported

References

1. Lulla RR, et al. *Sci Adv*. 2016;2(3):e1501354. **2.** Prabhu VV, et al. *Neoplasia*. 2020;22(12):725-744. **3.** López G, et al. *Acta Neuropathol Commun*. 2017;5(1):38. **4.** Karremann M, et al. *Neuro Oncol*. 2018;20(1):123-131. **5.** Ishizawa J, et al. *Cancer Cell*. 2019;35(5):721-737. **6.** Allen JA. et al. *Sci Transl Med*. 2013;5(171):171ra17. **7.** Ishizawa J, et al. *Sci Signal*. 2016;9(415):ra17.

Acknowledgments

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