Safety of ONC201 Administered Two Consecutive Days Per Week in Pediatric Patients With H3 K27M-mutant Glioma

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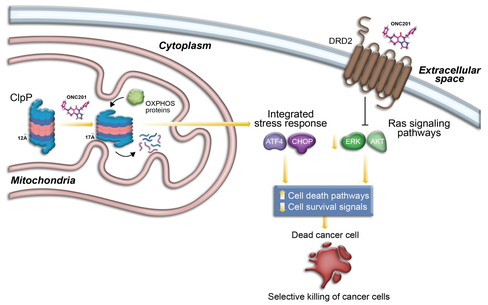
Background

- Gliomas harboring H3 K27M mutation exhibit dopamine receptor dysregulation[1]
- ONC201, an investigational oral anticancer small molecule, is a dopamine receptor D2/3 antagonist and a caseinolytic protease P agonist that crosses the blood brain barrier[2]

Figure 1. ONC201 Mechanism of Action[2-5]



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.

- The relevance of H3 K27M mutation to ONC201 anticancer activity was established by sustained tumor regressions and neurological improvements observed in the first few patients with gliomas that were treated with ONC201[6,7]
  - Treatment with ONC201 as a single agent in a registration cohort of patients with recurrent H3 K27M-mutant diffuse midline glioma induced durable tumor regressions by response assessment for neuro-oncology high-grade glioma criteria[2]
- ONC201 is being evaluated in pediatric patients with H3 K27M-mutant glioma and/or diffuse intrinsic pontine glioma (DIPG) in a dose-escalation and dose-expansion phase I trial[2]
- Although the recommended phase 2 dose (RP2D) of 625 mg ONC201 once weekly has been established as a biologically active dose that is well tolerated in adults as well as pediatric patients, twice per week dosing was also deemed to be safe in adults[8]
  - This warranted exploration of twice per week ONC201 dosing in pediatric patients with H3 K27M-mutant gliomas

Objective

- To explore safety and efficacy of ONC201 administered 2 consecutive days per week in pediatric patients with H3 K27M-mutant gliomas

Methods

Study Design

- Open-label, multi-arm, multi-center, phase 1 dose escalation and dose expansion ongoing trial (ONC014 study; NCT03416530) of ONC201 in pediatric patients with H3 K27M-mutant glioma and/or DIPG

Key Eligibility Criteria

- Pediatric patients (2–<19 years old)
- Karnofsky Performance Status (KPS)/Lansky score ≥50
- Presence of H3 K27M mutation in the tumor or agreement to post-mortem biopsy
- Completed ≥1 line of prior therapy
- No diffuse leptomeningeal disease or cerebrospinal fluid dissemination

ONC201 Dosing

- Dose escalation was performed by a 3 + 3 design beginning with two 125-mg capsules less than the adult RP2D of 625 mg equivalent based on body weight
- ONC201 was orally administered twice per week on 2 consecutive days (D1D2)
- One treatment cycle was 21 days (6 doses)

Table 1. ONC201 Dosing Scheme

Body weight, kg	ONC201 dose, mg*	ONC201 dose level, mg†		
		-1	1	2
10 to <12.5	145	NE	NE	125
12.5 to <27.5	197 to 289	NE	125	250
27.5 to <42.5	331 to 410	125	250	375
42.5 to <52.5	450 to 486	250	375	500
>52.5		375	500	635

*ONC201 dose equivalent of 625 mg adult dose. †ONC201 dose rounded to capsule strength. NE = not eligible because of body weight and capsule size.

Primary Endpoint

- Determine RP2D of ONC201 in twice per week schedule in pediatric patients with glioma

Secondary Endpoints

- Safety and tolerability, pharmacokinetics, and progression-free and overall survival

Results

Table 2. Demographic and Baseline Characteristics

Characteristic	Patients (n=12)
Age, y, median (range)	9 (4–18)
Female sex, n (%)	8 (66.7)
Race, n (%)	
White	9 (75.0)
Unknown	2 (16.7)
Other	1 (8.3)
Weight, kg, median (range)	34.7 (15.3–63.7)
KPS score, median (range)	80 (50–100)
Time from diagnosis, wk, median (range)	25.3 (13–56.3)
Primary tumor location, n (%)	
Pons	8 (66.7)
Thalamus	2 (16.7)
Midbrain	1 (8.3)
Spinal cord	1 (8.3)
Diagnosis, n (%)	
Diffuse midline glioma, H3 K27M mutant	8 (66.7)
DIPG (biopsied)	4 (33.3)
Non-DIPG (biopsied)	4 (33.3)
DIPG (non-biopsied)	4 (33.3)
Multifocal disease, n (%)	
Yes	4 (33.3)
No	8 (66.7)
Disease status, n (%)	
Post radiation, not recurrent	8 (66.7)
Recurrent	4 (33.3)
H3 K27M mutation, n (%)	
Immunohistochemistry	5 (41.7)
Next generation sequencing	3 (25.0)
H3.3 K27M mutation	3 (25.0)
H3.1 K27M mutation	0
Unknown	4 (33.3)
Number of recurrences, median (range)	0 (0–2)
Time from prior radiation, wk, median (range)	10.3 (4.1–41.4)
Re-irradiation, n (%)	1 (8.3)
Dexamethasone daily dose, mg, median (range)	2 (0–4)

DIPG = diffuse intrinsic pontine glioma; KPS = Karnofsky Performance Status.

Table 3. Summary of Safety

AE, n (%)	Patients (n=12)	
	All causality	Treatment-related*
Any AE	12 (100.0)	8 (66.7)
AE of grade ≥3	5 (41.7)†	0
AE leading to dose reduction	0	0
Serious AE	3 (25.0)	0
Dose-limiting toxicity	0	0

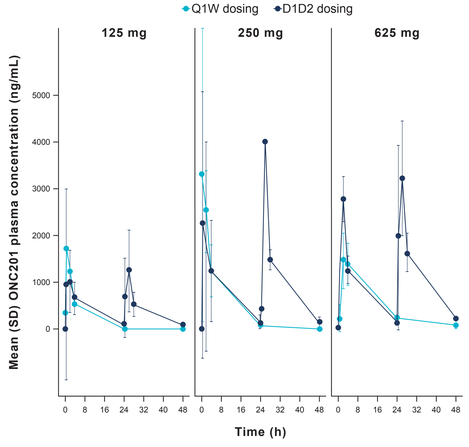
Data cut-off date: Oct 14, 2021. *All related AEs were grade 1 or 2. No related AEs were reported in >1 patient; terms included: ALT increase, amylase increase, AST increase, ataxia, diarrhea, face edema, fatigue, headache, hypertension, insomnia, lymphocyte count decrease, nausea, and weight increase. AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.

Table 4. Most Common Adverse Events

AE, n (%)	Patients (n=12)			
	All causality		Treatment-related	
	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue	7 (58.3)	2 (16.7)	1 (8.3)	0
Headache	7 (58.3)	0	1 (8.3)	0
Vomiting	6 (50.0)	0	0	0
Gait disturbance	4 (33.3)	3 (25.0)	0	0
Hyperglycemia	4 (33.3)	0	0	0
Hyponatremia	4 (33.3)	0	0	0
Nausea	4 (33.3)	0	1 (8.3)	0
Blood lactate dehydrogenase decreased	3 (25.0)	0	0	0
Decreased appetite	3 (25.0)	0	0	0
Lymphocyte count decreased	3 (25.0)	0	1 (8.3)	0
Pyrexia	3 (25.0)	0	0	0

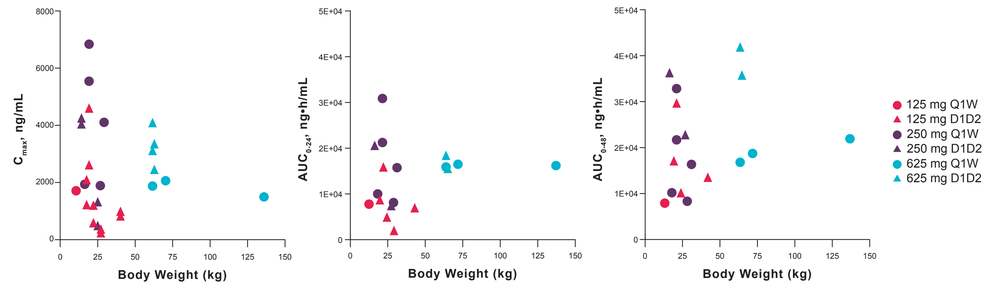
AE = adverse event.

Figure 2. Pharmacokinetics: ONC201 Plasma Concentration-Time Curves for Once and Twice Per Week Dosing*†



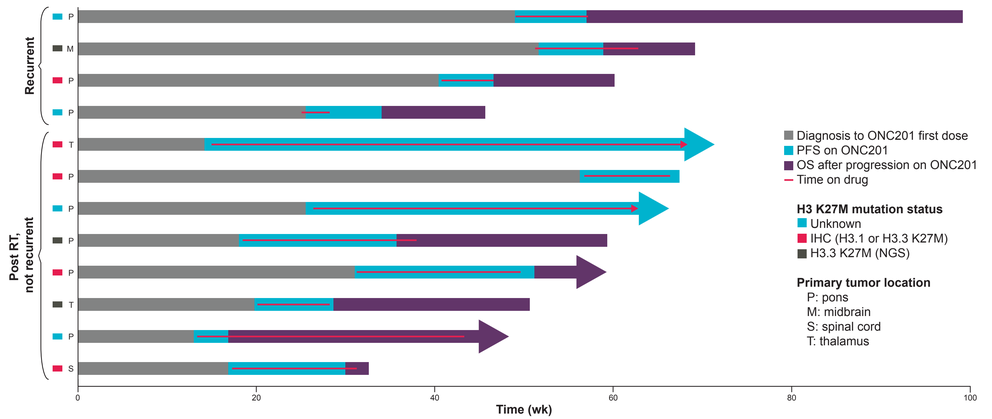
*Data for 375 mg and 500 mg dose were not calculated and reported because of incomplete sample collection. †Pharmacokinetic data from patients with Q1W dosing. D1D2 = twice per week on 2 consecutive days; Q1W = once per week; SD = standard deviation.

Figure 3. ONC201 Exposure by Body Weight*



*Pharmacokinetic data from patients with Q1W dosing. AUC = area under the curve; AUC_{0-24} = AUC from time zero to 24 h; AUC_{0-48} = AUC from time zero to 48 h; C_{max} = maximum plasma concentration; D1D2 = twice per week on 2 consecutive days; Q1W = once per week.

Figure 4. Clinical Outcomes



Data cut-off date: Oct 14, 2021. IHC = immunohistochemistry; NGS = next generation sequencing; OS = overall survival; PFS = progression-free survival; RT = radiation therapy.

Conclusions

- ONC201 was well tolerated at the adult 625-mg dose administered D1D2 scaled by body weight as a single agent in previously treated pediatric patients with H3 K7M mutant glioma
  - No instances of dose-limiting toxicity reported; grade ≥3 adverse events reported were gait disturbance and fatigue
- ONC201 exposure over 48 hours after intake (AUC_{0-48}) was greater with D1D2 dosing compared with once per week (Q1W) dosing (expected as D1D2 dosing provides 2x the dose vs Q1W dosing)
  - ONC201 dosing by body weight appears to result in similar exposure (AUC values) across doses; C_{max} appears to be greater in patients with lower versus higher body weight
- Two patients (post radiation therapy, not recurrent) remained on therapy for >1 year

Future Directions: A biopsy cohort of patients with twice per week dosing will be added to this study to determine ONC201 concentration in the tumor.

References

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