ONC018: Expanded Access to ONC201 for Patients with H3 K27M-mutant and/or Midline High Grade Gliomas

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CAUTION: Investigational New Drug

This document is a protocol for a human research study. This study is to be conducted according to the protocol, and applicable government regulations and Institutional research policies and procedures. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

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PROTOCOL SUMMARY

Sponsor: Oncoceutics

Title: Expanded Access to ONC201 for Patients with H3 K27M-mutant and/or Midline High Grade Gliomas

Protocol Number: ONC018

Objectives

Primary Objective

To provide expanded access to ONC201 for patients with previously-treated H3 K27M-mutant and/or midline high grade gliomas who cannot access ONC201 through clinical trials.

Secondary Objectives:

- To evaluate the safety and tolerability of ONC201.
- To document any efficacy of ONC201.

Study design

Multicenter, open-label, intermediate-size expanded access protocol

Dosing Regimen

Patients ≥18 years of age will receive ONC201 at the dose of 625 mg once every week.
Patients <18 years of age will receive ONC201 at a dose that is based on body weight.

Eligibility criteria

Each patient must be approved for enrollment in writing by Oncoceutics prior to initiation of ONC201 treatment.

Inclusion

1. Patient must have one type of diagnosis below:
    a. A glioma that is positive for the H3 K27M mutation (performed in a laboratory with CLIA certification);
    b. A grade III or IV glioma involving the thalamus, hypothalamus, brainstem, cerebellum, midbrain, or spinal cord;
    c. Diffuse intrinsic pontine glioma (DIPG), defined as tumors with a pontine epicenter and diffuse involvement of the pons. These patients are eligible with or without a tissue biopsy.
2. Unequivocal evidence of progressive disease on as defined by RANO criteria or have documented recurrent glioma on diagnostic biopsy.
3. Patient must have had previous therapy that includes radiotherapy.
4. Interval of at least 90 days from the completion of radiotherapy to the first dose of ONC201. If patients are within 90 days of radiotherapy, they may still be eligible if they meet one or more of the following criteria.
    a. Progressive tumor is outside the original high-dose radiotherapy target volume as determined by the treating investigator, or
    b. Histologic confirmation of tumor through biopsy or resection, or
    c. Nuclear medicine imaging, MR spectroscopy, or MR perfusion imaging

consistent with true progressive disease, rather than pseudoprogression or radiation necrosis obtained within 28 days of registration.

5. Patient must be at least 3 years of age.
6. Patient must weigh at least 10kg.
7. Patient must be able to swallow and retain orally administered medication. For patients unable to swallow capsules, oral ONC201 will be administered as a liquid formulation in Ora-Sweet.
8. From the projected start of scheduled study treatment, the following time periods must have elapsed from prior anti-cancer treatments: 5 half-lives from any investigational agent, 4 weeks from cytotoxic therapy (except 23 days for temozolomide and 6 weeks from nitrosoureas), 6 weeks from anti-cancer antibodies (except 21 days for bevacizumab), or 4 weeks (or 5 half-lives, whichever is shorter) from other anti-tumor therapies.
9. Contrast-enhanced head CT or brain MRI within 21 days prior to start of study drug.
10. Adequate organ and marrow function as defined below:
    a. Absolute neutrophil count ≥1,000/mm^3 without growth factor use ≤ 7 days prior to treatment (cycle 1 day 1, C1D1)
    b. Hemoglobin ≥8.0 mg/dL without red blood cell transfusion ≤ 3 days prior to C1D1
    c. Total serum bilirubin ≤1.5 X upper limit of normal (ULN)
    d. AST (SGOT)/ALT (SGPT) ≤2 X ULN; ≤ 5 X ULN if there is liver involvement secondary to tumor
    e. Serum creatinine ≤ 1.5 X ULN (OR creatinine clearance ≥ 60 mL/min/1.73 m^2)
11. For patients post pubertal: Female patients must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator.
12. Ability to understand a written informed consent document, and the willingness to sign it. Assent will be obtained when appropriate based on the subjects age.

Exclusion

1. Qualifies for participation in an ongoing ONC201 clinical trial or is already participating in an ONC201 clinical trial.
2. Current or planned participation in a study of an investigational agent or using an investigational device.
3. Evidence of diffuse leptomeningeal disease or CSF dissemination.
4. Any known systemic infection that, in the opinion of the investigator, could compromise the safety of the patient, while taking ONC201.

Efficacy will be recorded via the following endpoints:

- Progression-free survival
- Overall response rate
- Duration of response
- Overall survival
- Patient-reported outcomes
- Corticosteroid use

1 INTRODUCTION

This is an intermediate-size expanded access protocol to provide ONC201 to patients with previously-treated H3 K27M-mutant gliomas who cannot access ONC201 through clinical trials. Up to 100 evaluable patients will be treated under this protocol.

1.1 Indication

ONC201 is under development in clinical trials in patients with advanced cancer, including H3 K27M-mutant gliomas.

Gliomas in the midline of the brain are among the most aggressive types of primary malignant brain cancers. The disease arises from glial cells, which are cells that form the tissue that surrounds and protects other nerve cells found within the brain and spinal cord. H3 K27M refers to a specific mutation in proteins called histone H3 that frequently occurs in midline in midline gliomas and in young patients: ~75% of thalamic brain tumors, ~54% of brainstem tumors and 55% of spinal cord tumors; 24% of pediatric gliomas and 8% of adult gliomas. The H3 K27M mutation occurs in a unique spatiotemporal pattern, with midline gliomas involving the pons (i.e. DIPG) tending to occur in pediatric patients (<18 years of age) while midline gliomas involving the thalamus and spinal cord tending to occur in young adult patients.

Due to location in the brain, aggressiveness, and low survival time, gliomas in the midline of the brain have a dismal prognosis with a 2-year survival rate of <10%. The discovery of H3 K27M as an oncogenic mutation occurred in the context of midline gliomas that involve the thalamus, pons, spinal cord, and/or cerebellum and was first reported in publications in 2012. Since the midline region of the brain is involved in critical physiological functions, these tumors have historically been inoperable (especially in the brain stem where the pons is located). This means that until recently, midline gliomas such as diffuse intrinsic pontine glioma (DIPG) were diagnosed solely on a radiographic basis. Recent advances in neurosurgical techniques and increased patient consent to post-mortem tumor tissue retrieval led to the availability of sufficient biospecimens that enabled systematic molecular evaluations of DIPG and other midline gliomas.

Standard therapy for midline gliomas involves neurosurgery, if feasible, followed by fractionated external beam radiotherapy. Radiotherapy remains the sole standard-of-care alone that has been reported to prolong median survival by ~3 months.

The World Health Organization 2016 classification of central nervous system tumors defines diffuse midline gliomas with the H3 K27M mutation as a new distinct disease entity. Diffuse midline gliomas with this particular mutation are defined as Grade IV glioma under this criterion.

Since this is a newly defined disease, most of the prognostic literature for H3 K27M is derived from DIPG that exhibits a 70-85% prevalence of this mutation. It is clear than the presence of the H3 K27M mutation in tumors of the pons confers a much shorter overall survival relative to the minority of patients who do not have this mutation. For the smaller number of pediatric patients with gliomas outside of the pons, the literature is consistent that those with the H3 K27M mutation have a poorer prognosis. The field looks to DIPG as the most robust body of clinical experience with H3 K27M-mutant gliomas based on high prevalence of the mutation in that disease. Decades of DIPG clinical trials have failed to improve outcomes and standard-of-care, a 6-week course of

radiation, remains associated with a 9-11-month median overall survival. Historically, therapeutic clinical trials in DIPG focused on the evaluation of therapies that were proven effective in adult high-grade gliomas. The recent molecular profiling and emerging preclinical models of H3 K27M-mutant midline gliomas have shown that these tumors exhibit vastly different biology and therapeutic sensitivity relative to other adult gliomas, such as glioblastoma [1-3]

H3 K27M-mutant gliomas occur at a lower rate in adults compared to pediatric patients. The existing literature is relatively congruous with pediatric findings and overall seems to confirm the dismal effect of H3 K27M mutations in brain tumors for adults, especially in brainstem gliomas.

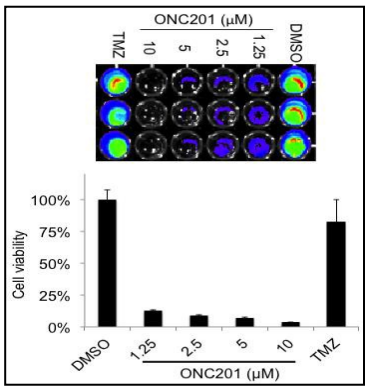


Figure 1.1. Cell viability of glioblastoma sample treated

1.2 Background on Study Agent

ONC201 is an anticancer small molecule that antagonizes dopamine receptor D2 (DRD2), a G protein-coupled receptor that is highly expressed in H3 K27M-mutant gliomas. ONC201 crosses the blood-brain barrier and has shown anti-tumor activity in non-clinical models of H3 K27M-mutant and other high grade gliomas. ONC201 is under evaluation in multiple Phase I and Phase II clinical trials for select advanced cancers following the definition of an adult recommended phase II dose of 625mg oral ONC201 every one week in a Phase I advanced solid tumor clinical trials in adults.

1.2.1 Preclinical Efficacy In High Grade Gliomas

ONC201 penetrates the blood-brain barrier, enabling its potential to address central nervous system tumors [4], unlike many available therapies. Animal studies have shown that ONC201 rapidly traverses the blood-brain barrier, achieves 5-fold higher concentrations in the brain relative to plasma and induces downstream signaling (TRAIL induction) in the brain. The compound is bioactive in the brain, shows no evidence of neurotoxicity, and is cytotoxic to high grade glioma tumors in vitro, ex vivo, and in vivo [4]. ONC201 has p53-indepenent activity against high grade glioma cell lines, including those with resistance to radiation. In addition to cell lines, ONC201 exerts anticancer activity in primary high-grade glioma samples resistant to temozolomide (Figure 1.1). In vivo, ONC201 shrinks temozolomide-resistant high-grade glioma xenografts and prolongs the survival of mice with orthotopic xenografts as a monoagent and in combination with bevacizumab (Figure 1.2). The single agent efficacy of ONC201 has also been observed in radio- and chemo-resistant high-grade glioma cell lines and in 3D neurosphere cultures of newly diagnosed and recurrent patient samples.

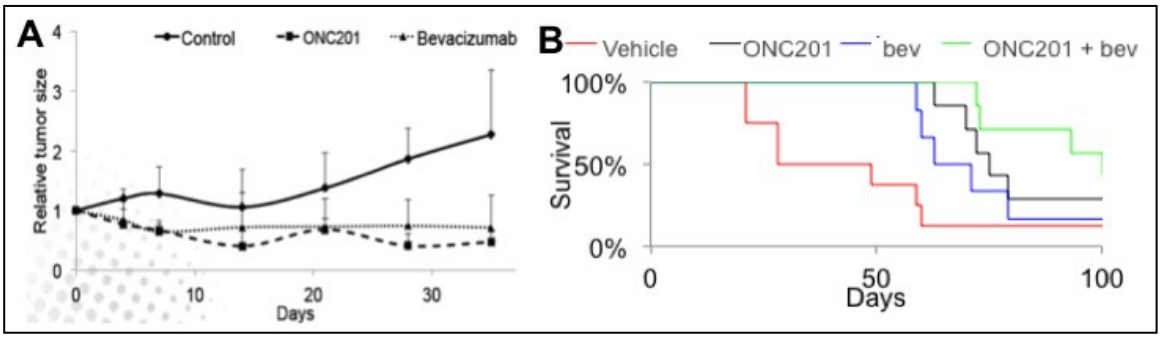


Figure 1.2. Overall survival of mice harboring SF767 intracranial tumors treated with a single oral dose of vehicle (n = 8), ONC201 (25 mg/kg, n = 7), bevacizumab (bev) (10 mg/kg, iv, n = 6), or ONC201and bevacizumab (n = 7) at 2 weeks after implantation.

In ChIP-Seq datasets, histone H3 and components of the PRC2 methyl transferase complex that is inhibited by the K27M mutation are physically associated with the DRD2 gene in DIPG and isogenic models [5-7]. We hypothesized that H3 K27M gliomas foster a chromatin landscape that leads to elevated DRD2 expression, which in turn may render these tumor cells more sensitive to ONC201. In support of this hypothesis, comparing ChIP-seq data in H3 K27M-mutant DIPG versus neural stem cell samples revealed a dissociation of H3 K27me3 from the DRD2 gene, that is associated with repressed gene expression. Accordingly, elevated DRD2 expression was detected by RNASeq in H3 K27M-mutant glioma samples compared to wild-type pediatric and adult glioma samples or H3 G34R mutant glioma (p=0.02; Figure 1.3). ONC201 was tested against a panel of patient-derived glioma tumorsphere cultures grown in serum-free neural stem cell media. Patient-derived lines included five histone H3 K27M-mutant DIPG (two HIST1H3B and three H3F3A mutant), two H3F3A G34 mutant pediatric glioblastoma (one G34V, one G34R), and 7 H3 wild-type (3 pediatric, 4 adult) glioblastoma cell lines. ONC201 was more potently cytotoxic to histone H3 K27M-mutant (median IC50 ~0.6 μM, n=5 lines) compared to histone H3 wild-type glioma lines (median IC50 ~1.5 μM, n=7 lines; p<.01).

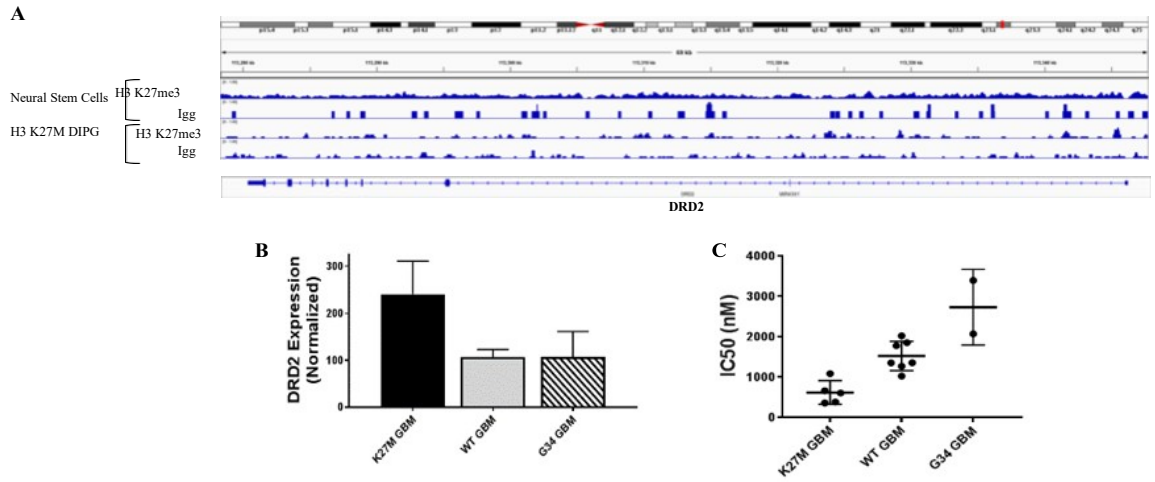


Figure 1.3. (A) Chip-Seq results for the association of H3 K27me3 with the DRD2 gene in H3 K27M-mutant DIPG cells and neural stem cells. (B) DRD2 expression and (C) ONC201 IC50 in a panel of H3 K27M mutant, wild-type and H3 G34 mutant glioma cell lines.

1.2.2 Mechanism of Action

ONC201 is a selective antagonist of the G protein-coupled receptor DRD2 that was identified through a phenotypic screen as a p53-independent small molecule inducer of TRAIL gene transcription in tumor cells. A series of gene expression profiling and cell signaling investigations have unraveled signaling pathways that are engaged in tumor cells following ONC201 treatment.

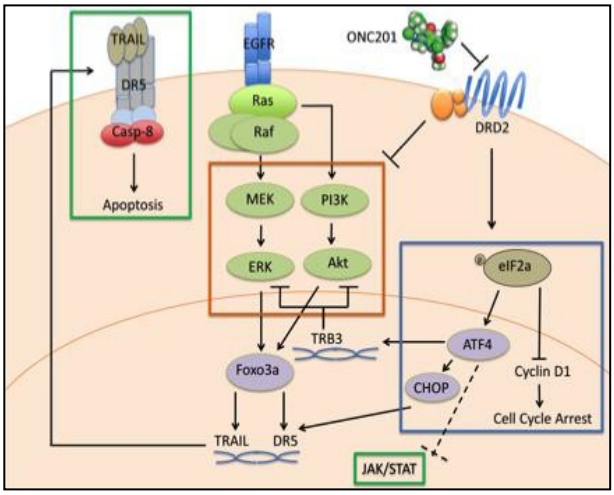


Figure 1.4 Proposed model of ONC201 in tumor cells.

Downstream of target engagement, ONC201 activates the integrated stress response (ISR), which is the same signaling pathway activated by ER stress-inducing compounds such as proteasome inhibitors (e.g. bortezomib). When the ISR is activated by ER stress-inducing compounds, the pathway is often referred to as the ER stress response. ONC201 causes an early-stage increase in the phosphorylation of eIF2-alpha at serine 51, which results in attenuation of protein translation and upregulation of the transcription factor ATF4 (Figure 1.4). ATF4 upregulates CHOP, which is also a transcription factor that regulates several apoptosis-related genes such as the TRAIL-receptor DR5. ATF4 and CHOP upregulate expression of TRB3, which interacts directly with Akt to decrease its kinase activity. TRB3 also serves as a scaffold protein in the MAPK signaling pathway that can negatively regulate this pathway. Decreased levels of phospho-MEK, -ERK, and -Akt have been documented in response to ONC201. The decreased ERK and Akt kinase activity results in less phosphorylated Foxo3a, which is a transcription factor that regulates both the TRAIL and DR5 genes. Dephosphorylated Foxo3a undergoes nuclear translocation and activation in response to ONC201.

In summary, ONC201 inhibits DRD2 to cause downstream activation of ATF4, which causes induction of genes that lead to apoptosis.

1.2.3 Nonclinical Safety/Toxicology Studies in Animals

In rats and dogs ONC201 was better tolerated when administered orally compared to intravenously. In rat non-GLP studies, the No-Observed Adverse Effect Level (NOAEL) was 225 mg/kg with oral administration compared to 100 mg/kg with a 2 hour infusion and 50 mg/kg with a 30 minutes infusion. Non-GLP clinical observations in rodents included decreased activity, altered gait, and mortality. In dog non-GLP studies, the NOAEL was at least 120 mg/kg with oral administration and clinical observations were limited to emesis and changes in fecal consistency.

The non-GLP studies only evaluated clinical observations, weight gain, food consumption and gross findings at necropsy. In general the toxicology/safety studies indicate that the acute toxicities associated with ONC201 are limited to the day of administration and are reversible.

In GLP dog studies, the NOAEL was at least 42 mg/kg. Observations were limited to decreased activity, decreased food consumption, emesis, salivation, and/or soft, loose or mucous feces. In rat GLP studies, the NOAEL was at least 125 mg/kg. Observations included decreased activity, decreased food consumption, decreased body weight, and abnormal stance and gait. Minor changes in serum chemistries were noted, largely in the 225 mg/kg rat cohort, which included slight increases in cholesterol and chloride. The significance of these findings is unknown as other clinical chemistry and histology did not corroborate this observation (e.g. liver findings). Rats receiving 125 or 225 mg/kg ONC201 had mild edema and inflammation that was primarily submucosal in the stomach and was completely resolved by day 19.

1.2.3.1 Non-GLP Safety Studies

Non-GLP studies were conducted in rats and dogs to assess clinical observations and body weight with ONC201.

Non-GLP toxicology studies in rats

The ability of rats to tolerate ONC201 by intravenous administration was explored as a function of infusion time. Clinical observations with intravenous administration included decreased activity, salivation, abnormal gait and stance, labored respiration, pale skin, nasal discharge, prostration during the dose, mild body twitching, and red discharge from the mouth.

The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 30-minute intravenous infusion was 50 mg/kg. The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 2-hour intravenous infusion was 100 mg/kg. Administration of 100 mg/kg ONC201 by intravenous infusion over 30 minutes resulted in the death of one male rat. Administration of 200 mg/kg ONC201 by a 2-hour infusion resulted in the death of both animals during the infusion period. Following these observations, the tolerance of oral ONC201 was explored given the potential to lower acute toxicity by lowering the maximal concentration (C_{max}). Clinical observations with oral exaggerated doses of ONC201 included decreased activity, abnormal gait and stance, prostration, irregular respiration, moderate twitching, red discharge on the muzzle, scant feces, hunched posture, not eating, piloerection, and skin cold to touch. The NOAEL following administration of ONC201 to Sprague-Dawley rats by oral gavage was 225 mg/kg.

Non-GLP toxicology studies in dogs

In parallel to non-GLP toxicology studies in rats, the ability of beagle dogs to tolerate ONC201 was explored. No deaths were observed at any doses in dogs. The NOAEL following the 30-minute intravenous infusion of ONC201 to beagle dogs is considered to be at least 33.3 mg/kg.

The 2 hour-intravenous infusion of 16.7 mg/kg ONC201 was not associated with any clinical signs of toxicity. Therefore the NOAEL following a 2 hour-intravenous infusion of ONC201 to beagle dogs is considered to be greater than 16.7 mg/kg, though higher doses were not explored as the oral route was selected for further development based on observations in rats. The NOAEL with oral ONC201 was considered to be at least 120 mg/kg in dogs. Clinical observations at doses of 66.7 to 120 mg/kg were limited to emesis and changes in fecal consistency.

1.2.3.2 GLP Toxicology and Safety Studies

Single Dose Oral Toxicity Study in Dogs (GLP)

A GLP study was performed to evaluate the toxicity and toxicokinetics of ONC201 following a single oral dose to Beagle dogs followed by a 2-day or an 18-day recovery period. Dogs received a single dose of 0, 4.2, 42, or 120 mg/kg by oral gavage. There was no mortality observed in this study. There were no definitive ONC201-related effects on group mean body weight or body weight gain, EKG rhythm or morphology, mean heart rate or arterial blood pressure, urinalysis, hematology parameters, coagulation parameters, clinical chemistry parameters, erythrocyte morphology, gross findings on necropsy, changes in absolute or organ to body or organ to brain weights.

Although not statistically significant, there were some dose-related decreases in group mean food consumption for the first week following dosing. The 120 mg/kg females had statistically significantly decreased group mean food consumption compared to the vehicle control group on Days 14, 15 and 18. There were no clinical signs of toxicity noted following a single dose of 4.2 mg/kg ONC201. At a dose of 42 mg/kg and 120 mg/kg, some dogs had clinical observations at approximately 1 hour post-dose including decreased activity, emesis, salivation, and/or soft, loose or mucous feces. Of uncertain relationship to ONC201 administration was the unusual finding of mononuclear cell inflammation in the blood vessels of the brain, which was multifocal and mild in one high dose female at Day 3, multifocal and minimal in one high dose female at Day 19, and minimal and focal in one control female at Day 19. Similar findings were not noted in any male animal.

Based on the results of this study, the NOAEL following oral administration of ONC201 at single doses of 4.2, 42 or 120 mg/kg to Beagle dogs is considered to be at least 42 mg/kg.

Single Dose Oral Toxicity and Toxicokinetic Study in Rats with a 19-Day Recovery and a 30-Minute Intravenous Infusion Toxicokinetic Arm (GLP)

A GLP study was performed to evaluate the toxicity of ONC201 following a single oral dose in Sprague-Dawley rats with necropsy after a 2-day or an 18-day recovery period. Rats received 0, 12.5, 125, or 125 mg/kg ONC201 by oral gavage.

There was no mortality observed in this study. There were no definitive ONC201-related effects on coagulation parameters, clinical chemistry parameters, gross findings at necropsy. There were

no clinical signs of toxicity noted at single doses up to 125 mg/kg ONC201. There were no ONC201-related statistically significant changes in hematology parameters or clinical chemistries outside of the historical control range for these values.

At a dose of 225 mg/kg, clinical signs of toxicity were limited on the day of dose administration to one out of twenty males and one out of twenty females that showed signs of decreased activity and abnormal gait and stance. The male was also noted to have increased respiration. All were normal by Day 2. No ONC201 related changes were noted during the functional observational battery (CNS activity) performed on Day 1 between 1 and 2 hr post-dose with the exception of one 225 mg/kg female noted as having decreased activity. A statistically significant decrease in group mean body weight gain was noted on Day 7 for the 225 mg/kg males. A statistically significant decrease in group mean food consumption was noted on Day 7 for the 225 mg/kg males.

On Day 3 the 225 mg/kg females also had increased glucose, cholesterol, sodium and chloride. Sodium and chloride were statistically significantly increased for the 125 mg/kg females. Only cholesterol and chloride were outside historical control ranges for this laboratory on day 19. As the increase in cholesterol was only noted for the females and no corresponding liver findings were observed, the significance of this finding is unknown. Though within normal historical control values for these laboratories, chloride remained increased for the 225 mg/kg males while cholesterol remained increased for the 225 mg/kg females.

Changes in brain and liver weights were noted but did not occur in a dose-dependent manner and no microscopic changes were noted in these organs for the high dose females. These changes were considered incidental and unrelated to treatment. At the Day 3 necropsy, ONC201-related minimal to mild edema and/or mixed cell inflammation was present in the non-glandular stomach of 225 mg/kg males and females. This edema and inflammation was primarily submucosal, although in some animals the inflammation involved the serosa or mesentery. Two males and one female had minimal focal ulceration of the overlying squamous epithelium. Similar stomach findings were seen in 125 mg/kg animals, with a lower incidence than in the 225 mg/kg group. There was complete resolution of all stomach lesions at the Day 19 necropsy, indicating full recovery.

Based on the results of this study, the NOAEL following oral administration of ONC201 at single doses of 12.5, 125 or 225 mg/kg to Sprague-Dawley rats is considered to be at least 125 mg/kg.

<u>Evaluation of the Effect of ONC201 Dihydrochloride on Respiratory Function Following Single-Dose Administration in Rats (GLP)</u>

A GLP study was performed to determine the potential effects of ONC201 dihydrochloride on respiratory function in rats following a single oral gavage administration. Twenty four (6/group) male rats received 0, 12.5, 125, or 225 mg/kg ONC201 by oral gavage and were monitored in plethysmographic chambers. The oral administration of ONC201 dihydrochloride at 12.5 and 125

mg/kg did not induce any biologically relevant effects on respiratory rate, tidal volume or minute volume in conscious male rats. A marginal to moderate transient decrease in respiratory rate and minute volume was observed following the oral administration of ONC201 dihydrochloride at 225 mg/kg, which resolved by 2 hours.

1.2.4 Pharmacokinetic Studies

1.2.4.1 Pharmacokinetic Studies in Animals

The measured half-life of ONC201 in mice is ~6 hours with intravenous administration as measured by an HPLC-UV assay. In rats, exposure to ONC201 was dose-dependent and approximately dose-proportional. Exposure to ONC201 was slightly greater in female rats after a single oral gavage dose. Plasma $t_{1/2}$ ranged from 2.3 to 8.4 hours in 7 of 8 profiles. Clearance ranged from 7.5 to 23.5 L/hr/kg in 7 of 8 profiles. Volume of distribution ranged from ~49 to ~103 L/kg in 6 of 8 profiles.

In dogs, exposure to ONC201 following oral gavage dosing at 4.2, 42, and 120 mg/kg ONC201 was dose-dependent and increased with greater ONC201 dose levels (Figure 1.5). Exposure to ONC201 was similar in male and female dogs with the observation that all mean male C_{max} and AUC values were slightly greater than the corresponding female values. Elimination of ONC201 from plasma was similar between the mid and high dose levels; mean $t_{1/2}$ ranged from 4.6 to 7.8 hours. Mean $t_{1/2}$ following the low dose of 4.2 mg/kg was ~1 hour [the half-life determined for dogs in the low dose group may represent more of a distribution phase half-life rather than the terminal plasma elimination half-life]. Overall elimination of ONC201 was greater following the low dose.

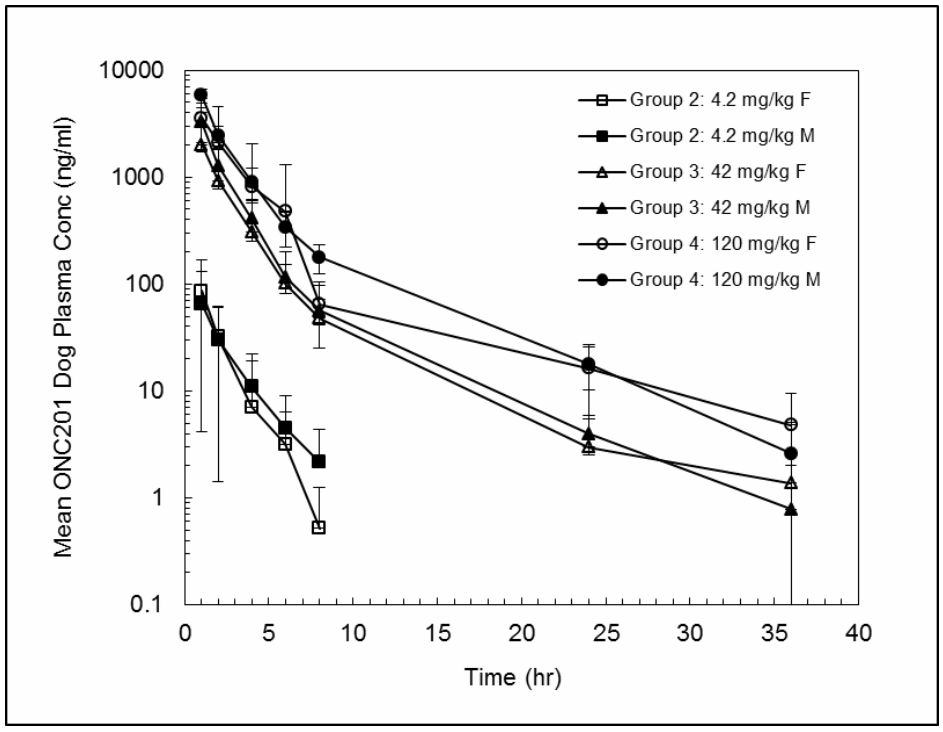


Figure 1.5 Dog Plasma Concentrations (Mean ± SD) of ONC201 Plotted as a Function of Time Following a Single Oral Gavage Dose to Male and Female Beagle Dogs.

1.2.4.2 Pharmacokinetic Studies in Humans

In Phase I advanced solid tumor adult patients who received ONC201 on a Q3W schedule, trends of increasing exposure with dose were consistent with dose proportionality. Patients receiving 625mg ONC201 exhibited a mean half-life of 11.3 h and achieved a mean Cmax of 3.6 ug/mL (~9.3 uM), which occurred at 1.8 hours following administration (Tmax) and surpassed the target Cmax of 1 ug/mL (Figure 1.6). The mean volume of distribution was 369 L, consistent with a large distributive volume and penetrance of target tissues observed in animals (Table 1.1).

Mean AUC was 37.7 h.µg/mL and mean CL/F was 25.2 L/h. Generally, CL/F was observed to be variable but consistent across all dose groups. There were no apparent relationships between drug CL/F and patient sex and age. Noticeable, shallow trends were observed with patient weight and BSA. An overall increase in CL/F was observed as weight and BSA increased. Although a slight upward trend was observed, there was no strong correlation between CL/F and CLCR (Table 6.1). Stronger correlations were observed with the distributive volume estimate and patient weight and BSA. An increase in volume of distribution was observed with increasing patient weight or BSA, as expected. Trends of decreasing exposure with increasing weight were observed in plots of Cmax/Dose and

AUC/Dose versus patient weight. Weight normalized CL/F was plotted versus Dose, showing a similar trend to un-normalized CL/F.

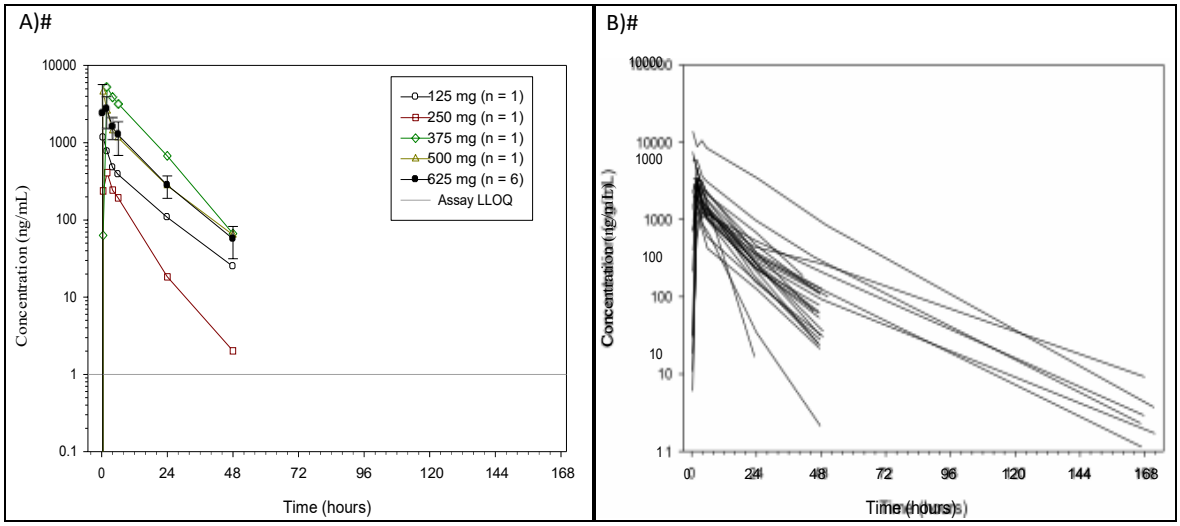


Figure 1.6 Mean ONC201 plasma concentrations versus time following the first dose of ONC201 in adult patients. Concentrations are shown as (A) mean for each dose cohort, or (B) for individuals treated at 625 mg.

Table 1.1. ONC201 pharmacokinetic parameters determined in patients after the first dose of 625mg ONC201 on a Q3W schedule (n=24).

	C_{max}	T_{max}	T_{lag}	AUC_{last}	λ_Z	$t_{1/2}$	AUC	V_Z/F	CL/F
	(ug/mL)	(h)	(h)	(h.ug/mL)	(h^{-1})	(h)	(h.ng/mL)	(L)	(L/h)
Mean	3.6	1.8	0.02	37.0	0.076	11.3	37.7	369	25.19
SD	2.6	0.9	0.08	41.6	0.046	5.2	41.6	193	14.22

With a Q1W schedule of ONC201, the PK profile of ONC201 during cycle 1 was consistent with previous experience on a Q3W schedule. Comparisons of the PK profile on the first day of cycle 1 (the first dose of ONC201) and cycle 2 (after the fourth ONC201 dose) revealed similar profiles with no significant differences in PK parameters (Table 1.2). Thus, weekly dosing of ONC201 does not appear to result in systemic accumulation or altered metabolism that alters its previously reported PK profile.

Table 1.2. Pharmacokinetic parameters for 625mg ONC201 on the first dose of cycle 1 and cycle 2 on a Q1W schedule (n=17).

	AUC(h.ug/L)		Cmax (ug/mL(		Tmax (h)		T1/2 (h)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Mean	42.6	42.6	3.6	3.2	1.4	1.9	9.8	9.1
SD	23.1	33.2	1.9	1.5	0.8	1.9	1.9	1.2

1.3 Clinical Studies

ONC201 is under development in several ongoing clinical trials in different types of advanced cancer in children and adults: H3 K27M-mutant glioma, other high grade gliomas, neuroendocrine tumors, endometrial cancer, breast cancer, multiple myeloma, acute leukemias, and non-Hodgkin's lymphoma. The objective of this protocol is to provide expanded access to ONC201 for patients with previously-treated H3 K27M-mutant and/or midline high grade gliomas who cannot access ONC201 through clinical trials.

1.3.1 Safety

ONC201 is being evaluated in multiple on-going clinical trials that are summarized in the Clinical Investigator's Brochure, along with the safety experience. As of June 21, 2018, 204 patients have been treated with ONC201: 93 patients were male and 111 were female. The age ranged from 3 to 91 years, (median: 61 years; mean 57.9 years). Sixty-three patients received ONC201 on a Q3W schedule, 137 patients received ONC201 on a Q1W schedule and 4 patients received ONC201 on a BIW schedule. The median number of doses administered per patient was 5 (range: 1-50): median 2 (range: 1-31) on a Q3W schedule, median 6 (range: 1-50) on a Q1W schedule and median 6 (range: 5-12) on a BIW schedule. Doses that were administered ranged from 125 mg to 625 mg. A total of 142 patients received 625 mg of ONC201 (the adult RP2D). The other 62 patients received doses of ONC201 less than 625 mg ranging from 125 mg to 500 mg.

ONC201 has been well tolerated across the various Phase I clinical trials and administration schedules with dose levels ranging from 125 mg to 625 mg. Only 1 dose reduction (625mg to 500mg) occurred in 1 patient with a Grade 3 neutropenia assessed by the PI as possibly related to ONC201. However, upon re-challenge neutropenia did not recur.

Some patients who received ONC201 have experienced mild or moderate adverse events that were attributed as possibly related to ONC201: fatigue, abdominal pain, fever, nausea, vomiting, anorexia, weakness, elevated serum amylase, neutropenia, bone pain, generalized weakness, allergic reaction, and ataxia.

The clinical trial that has enrolled the largest number of high grade glioma patients is NCT02525692 entitled "Oral ONC201 in Adult Recurrent Glioblastoma and H3 K27M-mutant Glioma." As of June 21, 2018, 41 patients with bevacizumab-naïve recurrent glioblastoma have received ONC201 as part of this trial. Baseline patient characteristics were a median age of 57 years (range: 20 to 80), 20 patients (49%) were male and 21 patients (51%) were female. Nine patients (32%) were 65 years or older while 32 patients (78%) were younger than 65 years of

age. Seventeen patients (42%) received 625mg ONC201 once every 3 weeks and 24 patients (58%) received 625mg ONC201 once every week. Adverse events, regardless of attribution, that occurred in >10 % of the patients in this trial are reported below.

Adverse Reactions	**NCT02525692 (N=41)**	
	All Grades %	**Grade 3-4 %**
Metabolism and Nutrition Disorders		
Hyperglycemia	37	0
Hypophosphatemia	32	2
Anorexia	10	0
Musculoskeletal and Connective Tissue Disorders		
Generalized muscle weakness	37	2
Nervous System Disorders		
Headache	34	0
Seizure	24	5
Memory impairment	17	0
Dizziness	10	0
Paresthesia	10	0
Dysphasia	7	0
Dysarthria	7	0
General Disorders		
Fatigue	32	2
Gait disturbance	24	5
Injury, Poisoning and Procedural Complications		
Fall	24	2
Psychiatric Disorders		
Confusion	12	0
Gastrointestinal Disorders		
Diarrhea	12	0
Nausea	10	0
Immune System Disorders		
Allergic reactions	7	0
Vascular Disorders		
Hypertension	7	2
Investigations		
Lymphocytes count decreased	5	2
Neutrophil count decreased	5	2
Infection and Infestations		
Lung infection	2	2

Urinary tract infection	2	2
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia	2	2
Respiratory failure	2	2

In summary, ONC201 was well tolerated in this study when administered once every week or once every three weeks at doses ranging from 125 mg to 625 mg.

1.3.2 H3 K27M-mutant Glioma

As of June 20, 2018, a cohort of 15 adult patients (≥18 years of age) with recurrent H3 K27M-mutant high grade glioma patients have been treated with ONC201 as participants in clinical trials or expanded access protocols. Demographics are described below in Table 1.3. This cohort excludes patients who are not eligible for either of the two current adult recurrent H3 K27M-mutant glioma trials for ONC201 (NCT03295396 and NCT02525692), i.e. excludes patients who had surgical intervention while on ONC201 or had leptomeningeal disease prior to receiving ONC201. All patients received 625mg oral ONC201 once weekly, except for one patient who received 625mg oral ONC201 once every three weeks.

Table 1.3: Demographics and clinical characteristics of adult recurrent H3 K27M mutant glioma patients without surgical intervention while on ONC201 who were evaluable for safety and efficacy (N=15). Patients with leptomingeal disease are excluded. All patients received 625mg ONC201. All patients received ONC201 once weekly, except for one patient who received ONC201 once every 3 weeks. *Indicates that the data is reported as the median with the range in parentheses.

Gender	
Male	6 (40%)
Female	9 (60%)
Age (years)*	34 (19-74)
Weight (kg)*	80.6 (57.1-123.8)
Baseline KPS	80 (50-90)
Histology	
Glioblastoma	2 (13%)
Gliosarcoma	1 (7%)
Astrocytoma, NOS	4 (27%)
Diffuse glioma, NOS	6 (40%)
Unspecified	2 (13%)
Primary tumor location	
Brain stem	4 (26%)
Basal ganglia	3 (20%)
Frontal lobe	1 (6.7%)
Spinal cord	1 (6.7%)
Thalamus	6 (40%)
Prior therapies	
Prior radiation	15 (100%)
Prior TMZ	15 (100%)

Prior lines of therapy	1 (1-4)
Baseline tumor size (cm^2)*	5.5 (2.6-32.2)
Baseline dexamethasone (mg/QD)*	3 (0-12)
Time from prior radiation to ONC201 initiation (months)	9.3 (1.5-23.2)

As of August 8, 2018, 10 of the 15 patients remain progression-free on ONC201 (median 3.8 months, range 1.4-27.3 months), 2 patients have had radiographic progression but remain on ONC201 (3.8 and 9.1 months), and 3 patients are off study and have died. Among this cohort, the median progression-free survival (PFS) has not been reached with a median follow-up of 3.5 months (range 0.8-27.3 months) (Figure 1.7).

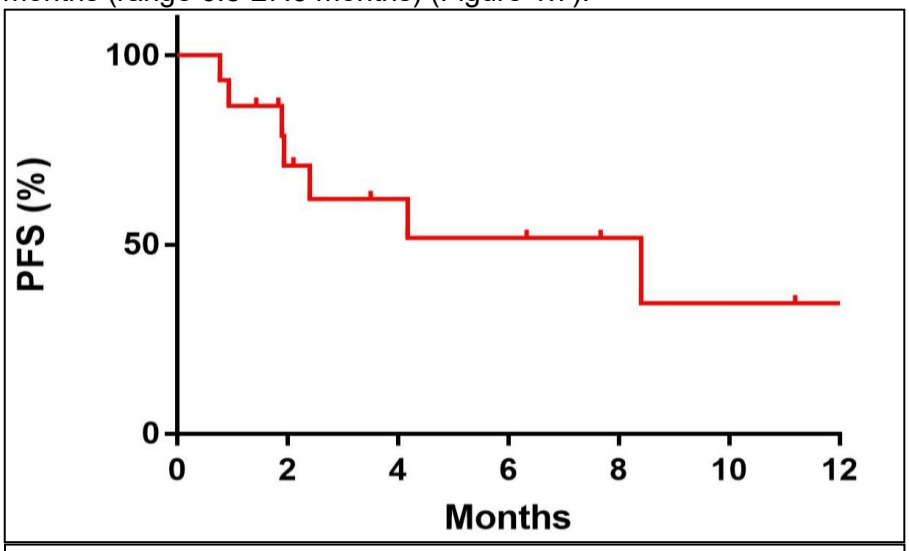


Figure 1.7. Progression-free survival of adult recurrent H3 K27M-mutant glioma patients treated with ONC201. Cut-off date is August 8, 2018.

As of August 8, 2018, fourteen of 15 patients have had at least one on-treatment MRI with investigators reporting tumor measurements and response evaluation by RANO criteria. Four of these 14 patients have shown >50% regression relative to baseline that remains durable (9.4 month median follow-up from first dose; 3.5-27.3 months) (Figure 1.8). By RANO criteria, three patients had a Partial Response, 1 patient did not have measurable disease at baseline (multi-focal lesions <1cm), 6 patients had stable disease, and the remaining 4 patients had progressive disease. This yields a disease control rate (SD+PR+CR) of 71% and an objective response rate (PR+CR) of 23%.

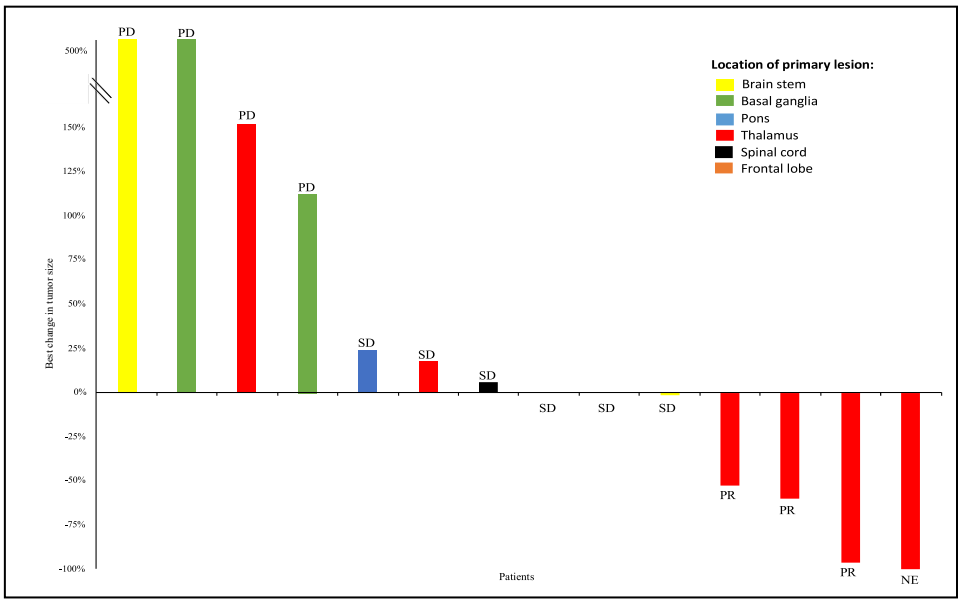
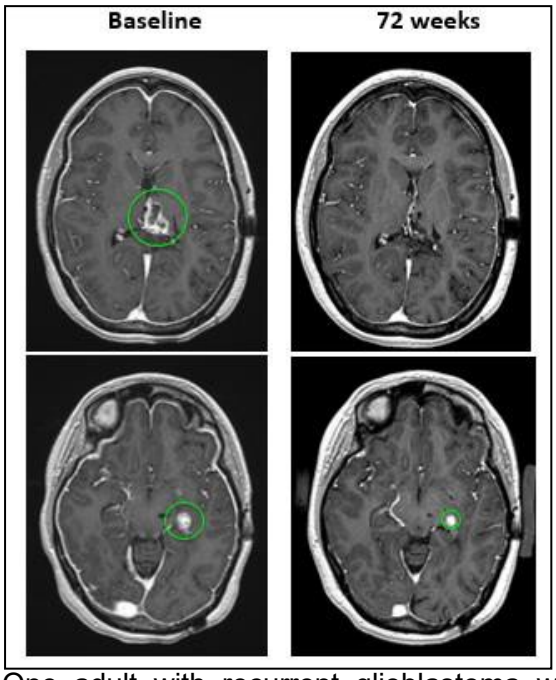


Figure 1.8. Waterfall plot for adult recurrent H3 K27M-mutant glioma patients treated with ONC201. Cut-off date is August 8, 2018. Change in tumor size calculated as the best on-treatment change in the sum of products of perpendicular diameters of all measurable enhancing lesions compared with baseline. PD – progressive disease by RANO; SD – stable disease by RANO; PR – partial response by RANO; NE – not evaluable for response by RANO (<1cm multi-focal lesions).

In addition to radiographic improvements, potential clinical improvements in neurological symptoms and quality of life have been reported in some patients. Radiographic and clinical benefits in the 4 patients with >50% regressions in thalamic tumors are summarized below, along with a brief medical history.



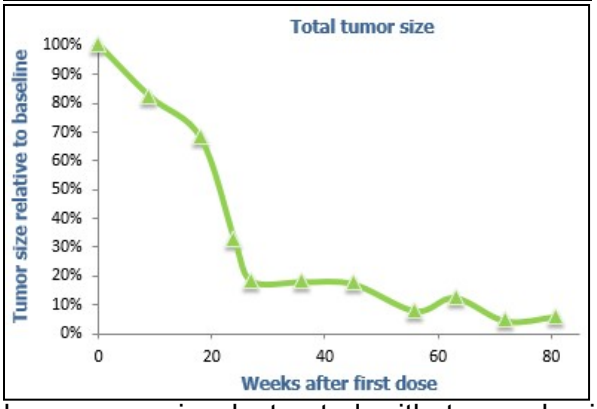


Figure 1.9. Gadolinium-enhanced MRI at baseline and 72 weeks post-ONC201 initiation of 2 lesions in a recurrent H3 K27M-mutant glioma patient who received ONC201 at 625 mg on a Q3W schedule. Total tumor size relative to baseline is shown for the duration of ONC201 administration.

One adult with recurrent glioblastoma who was previously treated with temozolomide and radiation has exhibited a 96% reduction in tumor size relative to baseline, including a complete regression of the primary thalamic lesion (Figure 1.9). This partial response remains durable after first being achieved at 4.9 months following ONC201 initiation, and the patient continues on ONC201 for > 27 months. This patient previously received 5940 cGy radiation in combination with temozolomide 75 mg/m^2 that began on October 4, 2015 and concluded on November 13, 2015. She previously completed 4 adjuvant cycles of monthly temozolomide 150 mg/m^2. The dose was not escalated to 200mg/m^2 until her fourth cycle of temozolomide because of complaints of fatigue. She developed progression on March 17, 2016 and initiated 625mg ONC201 once every three weeks on March 31, 2016.

Another adult with recurrent glioblastoma has shown complete elimination of her malignant lesions in the thalamus and caudate (Figure 1.10). There is one remaining T1-bright lesion that has not changed in appearance since initiating ONC201 and appears to be related to a prior stroke (i.e. not malignant). This patient was diagnosed with H3 K27M-mutant glioblastoma. The patient received 5400 cGy radiation in combination with temozolomide from November 20, 2015 to January 5, 2016. Concurrent temozolomide was discontinued early in December 2015 for Grade 1 thrombocytopenia. She completed 6 cycles of adjuvant temozolomide from February 22, 2016 to July 20, 2016. Her course has been complicated by a right basal ganglia infarct discovered in October 2016 and two additional suspected strokes in left frontal periventricular white matter and left corona radiata on 11/30/2016. Imaging from January 2017 was with more prominent enhancement in the left corona radiata and new enhancement in the left caudate, consistent with progression of disease. Due to progression, CCNU was administered from February 9, 2017 to May 9, 2017 at the following doses: 90mg/m2 on February 9, 2017; 67.5/m2

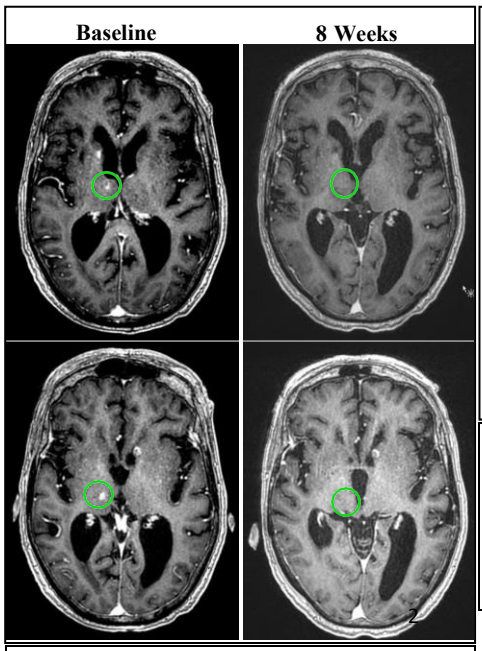


Figure 1.10. Gadolinium-enhanced MRI at baseline and 8 weeks post-ONC201 initiation in a recurrent H3 K27M-mutant glioma patient who received ONC201 at 625 mg on a Q1W schedule.

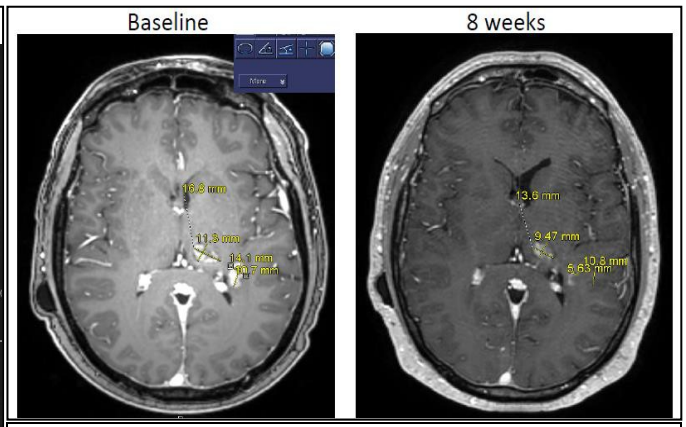


Figure 1.11. Gadolinium-enhanced MRI at baseline and 8 weeks post-ONC201 initiation in a recurrent H3 K27M-mutant glioma patient who received ONC201 at 625 mg on a Q1W schedule.

on March 21, 2017; 67.5mg/m^2 on May 9, 2017. MRI on July 20, 2017 revealed new enhancing lesion in the right caudate that was concerning for progression of disease. The patient enrolled on the ONC006 trial (NCT02525692) on August 23, 2017 receiving 625mg ONC201 orally once weekly. Baseline MRI showed multi-focal disease involving the thalamus and caudate with <1cm that deemed the disease not measurable for response by RANO criteria. The patient was not receiving steroids at baseline and has not begun steroids while on treatment. MRI evaluation after 8 weeks revealed a disappearance of three lesions and one remaining lesion in the caudate. This lesion is a T1-bright that may be related to a prior stroke. Subsequent MRIs have continued every 8 weeks with the same appearance and the patient remains on single agent ONC201 for 11.2 months.

Another adult with recurrent H3 K27M-mutant glioma has exhibited a 60% reduction in tumor size relative to baseline, including a complete regression of the primary thalamic lesion (Figure 1.11). This patient is a 38-year-old who was diagnosed with a Grade 3 anaplastic astrocytoma with the H3 K27M mutation in the left thalamus in December 2016. The patient began temozolomide (75mg/m^2/day for 42 consecutive days) and radiation (60 Gy) on December 29, 2016. He required accelerated fraction form 200cGy to 250 cGy daily dose after 3000 cGy in light of his progress disease. He completed radiation to the left thalamus on February 3, 2017. He completed 6 weeks of temozolomide, finishing the final 6th week after completing the accelerated radiation schedule. He resumed temozolomide on March 6, 2017 at a dose of 150mg/m^2 that was increased to 200mg/m^2 on April 3, 2017. The last dose of TMZ was July 28, 2017. MRI evaluation in August 2017 revealed progressed disease. The patient began CCNU at 110mg/m^2. After 2 cycles, MRI evaluation on October 6, 2017 revealed further progression of infiltrative edema and small contrast-enhancing lesions with spectroscopy and perfusion characteristic on neoplasm, without new mass effect or herniation. The patient began ONC201 via a compassionate use emergency protocol on November 2, 2017 receiving 625mg ONC201 orally once every week. At baseline,

this patient was on 60mg daily hydrocortisone, plus 10mg prednisone and would take dexamethasone for headaches up to 8mg daily. His first MRI on December 11 after 6 weeks of starting ONC201 showed improved left lateral periatrial enhancement and edema, as well as a 34% overall regression. Subsequent MRIs in February and April of 2018 have shown >50% regression that represents a partial response by RANO criteria. The patient has reported potential clinical improvements in disease-related symptoms such as headaches, nausea, and right-sided numbness. The patient continues ONC201 for > 9.1 months.

Another adult with recurrent H3 K27M-mutant has exhibited a 53% reduction by RANO in tumor volume relative to baseline (Figure 1.12), 15 weeks after beginning ONC201. This patient was diagnosed with WHO Grade IV diffuse midline glioma on December 4, 2017. This patient was treated with 6000 cGy radiation in combination with temozolomide 75 mg/m^2 that began on January 3, 2018 and concluded on February 13, 2018. The patient began 625mg ONC201 orally once every week on March 29, 2018. The patient began Avastin (every three weeks) beginning May 10, 2018 to taper steroids. The patient continues on ONC201 for >3.5 months.

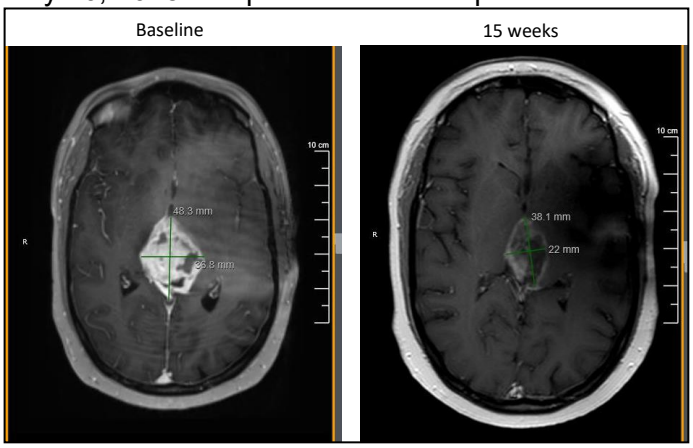


Figure 1.12. Gadolinium-enhanced MRI at baseline and 15 weeks post-ONC201 initiation in a recurrent H3 K27M-mutant glioma patient who received ONC201 at 625 mg on a Q1W schedule.

1.4 Rationale for Expanded Access

ONC201 is being evaluated in several clinical trials that enroll H3 K27M-mutant and/or midline high grade gliomas. Patients eligible for these trials include adults with recurrent disease and pediatric patients with newly diagnosed or previously treated H3 K27M and/or DIPG. This protocol is intended to provide expanded access to ONC201 for patients with previously-treated H3 K27M-mutant and/or midline high grade gliomas who cannot access ONC201 through clinical trials.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

To provide expanded access to ONC201 for patients with previously-treated H3 K27M-mutant and/or midline high grade gliomas who cannot access ONC201 through clinical trials.

Secondary Objectives

- To evaluate the safety and tolerability of ONC201.
- To document any efficacy of ONC201.

2.2 Outcome Measures/Endpoints

2.3.1 Efficacy

- Progression-free survival
- Overall response rate
- Duration of response
- Overall survival
- Patient-reported outcomes
- Corticosteroid use

2.3.2 Safety

- Adverse events
- Laboratory evaluations
- KPS status
- Vital signs
- Physical examinations

3 STUDY DESIGN

Multicenter, open-label intermediate size expanded access protocol; up to 100 evaluable patients will be treated under this protocol.

3.1 Dose and Planned Scheme

Treatment with ONC201 will be administered once every week at 625 mg for patients ≥18 years of age, or a dose that is based on body weight for patients <18 years of age. One cycle is defined as 28 days (four weeks), with day 1 defined as the day of study drug administration. ONC201 will be provided as an oral capsule or liquid formulation. The patient may discontinue therapy at any time for any reason.

Oncoceutics should be consulted prior to any schedule modifications or the addition of other therapies.

3.2 Study Schedule Overview

Note that the procedures below should be completed as per standard of care and/or as per the treating physician's discretion. One treatment cycle will be defined as 28 days (4 weeks).

	Screening / Baseline	Treatment Cycles	Disease Assessment Cycles	End of Treatment	Follow-up
	Within 14 days of Treatment	**Every 4-8 weeks[11] (+/-3 days)**	**Every 8 weeks (56 +/- 7 days)**	**(30 +/- 7 days post last dose)**	**(30 +/- 7 days post last dose)**
Informed Consent	X				
Demographics	X				
Inclusion/Exclusion Criteria	X				
Medical/Disease history, including prior MRI scans[13]	X				
KPS or Lansky assessment	X				
Archival tumor tissue[1]	X				
Physical exam, Neurologic exam	X	X		X	
Vital signs[2]	X	X		X	
Hematology[3]	X	X		X	
Serum chemistries[4]	X	X		X	
12 Lead ECG	X				
Coagulation tests[5]	X			X	
Pregnancy test[6]	X			X	
MDASI[12]	X	X		X	
Disease assessment[7]	X	X	X	X	
Corticosteroid Use	X	X	X	X	
Adverse Event Assessment[8]		→	→	→	
Concomitant medications		→	→	→	
ONC201 Dispensation[9]	X	X			
Survival[10]				X	X

1. Obtain archival tumor tissue at the time of enrollment, if available.
2. Vital signs: Height (required only at screening), weight, blood pressure, respiration, pulse, oral temperature. Determine if significant weight loss or gain (±10%).
3. Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
4. Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, random glucose, albumin, total protein, creatinine, blood urea nitrogen, uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, lactate dehydrogenase (LDH).
5. Coagulation tests (required at screening only): PT/INR, PT, PTT
6. Pregnancy Test – As applicable: baseline within 14 days of start of treatment and at end of study - urine or serum β-HCG in women of child bearing potential.
7. Neuroimaging (disease assessments). Contrast-enhanced MRI disease assessments will be performed as standard of care (e.g. every 8 weeks) until patients come off study. Screening/Baseline neuroimaging disease assessments may be completed up to 21 days before first dose.
8. All adverse events will be recorded from the time the date of initiation of study therapy through 30 days following cessation of treatment and at each examination. Serious Adverse Events will be followed through 90 days following cessation of treatment.
9. ONC201 Dispensation. At the C1D1 visit and at each treatment cycle (every 4 weeks), subjects will be given a supply of ONC201 for administration at home until the next treatment or scheduled visit. For patients also receiving radiation, ONC201 should be taken on Mondays assuming that radiation is administered on a Monday through Friday schedule.
10. All subjects will be followed post-treatment until death, withdrawal of permission to record at least survival data, or subject is lost to follow-up every 30 days (±7 days) after coming off study.
11. If a patient completes 6 cycles without major (grade 3-4) ongoing toxicity or protocol non-compliance, the patient may be seen every 8 weeks for routine assessment of physical exam, hematology, chemistries and AE/concomitant medication assessment. The window of the every 8 week assessment is +/-7 days.
12. For patients >18 years of age.
13. In addition, provide imaging assessments from initial diagnosis, surgery planning, post-surgical, post chemoradiation, scheduled and unscheduled MRIs.

3.3 Contraception

Female patients of child-bearing potential must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator. These restrictions should remain in force for 90 days from the last dose of investigational agent.

Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. The definition of effective contraception should be in agreement with local regulation and based on the judgment of the principal investigator or a designated associate. A suggested definition of adequate contraception is the use of double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device).

4 STUDY POPULATION

4.1 Subject Inclusion Criteria

1. Patient must have one type of diagnosis below:
    a. A glioma that is positive for the H3 K27M mutation (performed in a laboratory with CLIA certification);
    b. A grade III or IV glioma involving the thalamus, hypothalamus, brainstem, cerebellum, midbrain, or spinal cord;
    c. Diffuse intrinsic pontine glioma (DIPG), defined as tumors with a pontine epicenter and diffuse involvement of the pons. These patients are eligible with or without a tissue biopsy.
2. Unequivocal evidence of progressive disease on as defined by RANO criteria or have documented recurrent glioma on diagnostic biopsy.
3. Patient must have had previous therapy that includes radiotherapy.
4. Interval of at least 90 days from the completion of radiotherapy to the first dose of ONC201. If patients are within 90 days of radiotherapy, they may still be eligible if they meet one or more of the following criteria.
    a. Progressive tumor is outside the original high-dose radiotherapy target volume as determined by the treating investigator, or
    b. Histologic confirmation of tumor through biopsy or resection, or
    c. Nuclear medicine imaging, MR spectroscopy, or MR perfusion imaging consistent with true progressive disease, rather than pseudoprogression or radiation necrosis obtained within 28 days of registration.
5. Patient must be at least 3 years of age.
6. Patient must weigh at least 10kg.
7. Patient must be able to swallow and retain orally administered medication. For patients unable to swallow capsules, oral ONC201 will be administered as a liquid formulation in Ora-Sweet.

8. From the projected start of scheduled study treatment, the following time periods must have elapsed from prior anti-cancer treatments: 5 half-lives from any investigational agent, 4 weeks from cytotoxic therapy (except 23 days for temozolomide and 6 weeks from nitrosoureas), 6 weeks from anti-cancer antibodies (except 21 days for bevacizumab), or 4 weeks (or 5 half-lives, whichever is shorter) from other anti-tumor therapies.
9. Contrast-enhanced head CT or brain MRI within 21 days prior to start of study drug.
10. Adequate organ and marrow function as defined below:
    a. Absolute neutrophil count ≥1,000/mm^3 without growth factor use ≤ 7 days prior to treatment (cycle 1 day 1, C1D1)
    b. Hemoglobin ≥8.0 mg/dL without red blood cell transfusion ≤ 3 days prior to C1D1
    c. Total serum bilirubin ≤1.5 X upper limit of normal (ULN)
    d. AST (SGOT)/ALT (SGPT) ≤2 X ULN; ≤ 5 X ULN if there is liver involvement secondary to tumor
    e. Serum creatinine ≤ 1.5 X ULN (OR creatinine clearance ≥ 60 mL/min/1.73 m^2)
11. For patients post pubertal: Female patients must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception while taking ONC201 and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator.
12. Ability to understand a written informed consent document, and the willingness to sign it. Assent will be obtained when appropriate based on the subjects age.

4.2 Subject Exclusion Criteria

1. Qualifies for participation in an ongoing ONC201 clinical trial or is already participating in an ONC201 clinical trial.
2. Current or planned participation in a study of an investigational agent or using an investigational device.
3. Evidence of diffuse leptomeningeal disease or CSF dissemination.
4. Any known systemic infection that, in the opinion of the investigator, could compromise the safety of the patient, while taking ONC201.

5 STUDY TREATMENT

5.1 Treatment Regimen

After screening procedures and registration, all subjects will be treated with study treatment, which should begin as close as possible to the date on which the participant is registered. ONC201 will be administered in an outpatient setting. Patients ≥18 years of age will receive ONC201 at the dose of 625 mg once weekly.

Patients <18 years of age will receive ONC201 at a dose that is based on body weight, as outlined below. The body weight of patients will be rounded to the near 5kg interval to use the dose chart below. Patients who are <10kg are not eligible to receive the drug at any dose level.

Table 5.1 ONC201 dose for patients <18 years of age.

Patient body weight (kg)	ONC201 dose (mg)
10-12.4	125
12.5-27.4	250
27.5-42.4	375
42.5-52.4	500
52.5+	625

ONC201 will be provided as an oral capsule at a strength of 125mg per capsule (alternative strengths may be manufactured in the future). For doses that occur on days where a clinic visit is not scheduled, subjects may take the medication at home.

5.2 Drug Supply

5.2.1 Formulation, Packaging and Storage

The study drug ONC201 is provided as a dihydrochloride salt (125 mg free base; ~150mg disalt), along with microcrystalline cellulose (MCC), filled into hydroxypropyl methylcellulose (HPMC) capsule shells.

The ONC201 drug product capsules are intended for oral administration. The product is stored in a multi-dose container. The capsules are packaged in high-density polyethylene (HDPE) white opaque bottles, closed with an induction seal and capped with a white ribbed SecuRx® polypropylene (PPE) cap. The capsules are to be stored in the original closed container at room temperature (15 to 30°C).

The study drug bottle label bears the following information:

ONC201 Capsules, 125mg

For Oral Use Only

Caution: New Drug--Limited by Federal (or United States) law to investigational use.

Storage: Preserve in original tightly closed containers at room temperature (15 to 30°C)

Sponsor: Oncoceutics, Inc

Batch # xxx-xxx-xxxx-xx **Mfg date: XX-XXXX**

Figure 5.1: Investigational drug label

5.2.2 Drug Accountability

Upon receipt at the investigative site, study drug product must be stored at room temperature in the original packaging. The drug should be protected from light and excessive humidity in a monitored, locked, secure area with limited access. Storage area temperature conditions must be

monitored and recorded daily. All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. Study site staff must instruct patients on how to store and administer oral study drug agents that are dispensed for at-home administration.

Accountability for study drug product is the responsibility of the investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient-by-patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. A written explanation must be provided for any discrepancies. Patients are to be instructed on proper accountability of the take-home study drugs and will be instructed to return any unused drug in the original packaging along with their completed diary cards at the appropriate clinic visits. The investigator must destroy or return all unused drug product provided.

5.3 ONC201 Administration

The study drug, ONC201, will be supplied in capsule form for oral dosing. The product may be dissolved into Ora-sweet for those patients unable to swallow capsules, see below.

Subject should take the designated number of capsules of ONC201 at approximately the same time on each day of drug administration. Subject will be instructed to not eat for 2 hours before and after dosing.

ONC201 should be taken with a glass of water and consumed over as short a time as possible. Subject should swallow the capsules as a whole and not chew them. Do not crush or empty the capsule. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted as an adverse event. In addition, on the days of drug administration the exact time of any episodes of vomiting within the first 4 hours post-dosing on that day must be noted whenever possible.

For the liquid formulation, the investigational pharmacy will dissolve the number of ONC201 capsules indicated in the dosing table above into Ora-Sweet at a concentration of 4-40mg/ml with vortexing. Capsules of ONC201 can be opened and the contents of the capsule transferred to amber plastic oral prescription bottles with child-resistant caps. Solutions should be prepared so that only one dose of ONC201 is contained per bottle (i.e. one bottle per week). After administration of the entire contents of the bottle, 1 tablespoon of water or Ora-Sweet should be added to the container, shaken for 10 seconds, and the entire contents of the bottle should be consumed by the patient. The solution may be dispensed for use within 8 weeks from preparation.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue once every week until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

- The Sponsor or the treating physician chooses to discontinue the study

Given the limited options and the safety profile of ONC201, treatment may continue following disease progression at the discretion of the patient and the treating physician.

6 DOSING DELAYS/DOSE MODIFICATIONS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. Below are dose modifications for adverse events that are attributable to study drug, including: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia – only if associated with clinically significant bleeding. If a patient experiences other adverse events, or several adverse events and there are conflicting recommendations based on Grade, the investigator will use the recommended dose adjustment that reduces the dose. Dose modifications will be made based on an adverse event that occurs during any time during a cycle.

Dose modifications are per the clinical judgment of the investigator and agreement of the subject, the treatment will be resumed according to the table below. Dose modification may not be required for adverse events that are clinically manageable.

Dose adjustment rules for Adverse Events (AEs), including Nausea, Diarrhea, Neutropenia, Thrombocytopenia - only if associated with clinically significant bleeding, and Other AEs. Alopecia does not require dose adjustments.

CTCAE Grade	Management/Next Dose for ONC201
≤ Grade 2	No change in dose
Grade 3 or 4*	Hold until < Grade 2. If resolved to < Grade 2 within 7 days, resume dosing at 500mg if previously dosed at 625mg or resume dosing at 375mg if previously dosed at 500mg.**
*Patients requiring a delay of >3 weeks should go off protocol therapy. Patients with grade 3 neutropenia associated with fever should also go off therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Table 6.1: Dose Modifications for those patients <55kg:

Patient body weight (kg)	ONC201 (mg) equivalent of 625mg adult dose	ONC201 (mg) Starting Dose	First reduced Dose	Second reduced Dose
10	145	125	See Note	See Note
15	197	250	125	See Note
20	250	250	125	See Note

Patient body weight (kg)	ONC201 (mg) equivalent of 625mg adult dose	ONC201 (mg) Starting Dose	First reduced Dose	Second reduced Dose
25	289	250	125	See Note
30	331	375	250	125
35	372	375	250	125
40	410	375	250	125
45	450	500	375	250
50	486	500	375	250
>52.5	625	625	500	375

Note: Please contact the study sponsor if the patient requires a dose escalation that is not defined above.

Participants who experience an adverse event that requires a treatment delay or dose reduction should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution; if the adverse event does not resolve within 3 weeks, the interval for testing may be reduced after consultation and written approval by the Overall Principal Investigator (or his designee).

For holds for reasons other than treatment related toxicities, if the participant does not meet criteria to resume treatment within 6 weeks of the event precipitating the hold, the study agent(s) may be restarted with approval from the overall Principal Investigator or designee, as long as there has been no significant evidence of disease progression (e.g., by clinical findings, symptoms, tumor markers) during the treatment interruption.

6.1 Concomitant Medications

The addition of anti-cancer therapies or devices to single agent ONC201 is not permitted without consultation and written approval from Oncoceutics. The use of bevacizumab solely for treatment of radiation necrosis, pseudoprogression, or tapering of corticosteroids is allowed.

The potential of ONC201 to induce human cytochrome P450 (CYP) isozymes CYP1A2, 2B6, and 3A4 has been evaluated in human hepatocytes. Under the experimental conditions, ONC201 showed no significant induction potential for CYP 1A2 and 3A4. ONC201 showed modest induction of CYP2B6 mRNA expression (2-4 fold; 9.1-17.8% of positive controls) in two out of three donors.

No formal drug-drug interactions with ONC201 or any metabolites have been performed. These studies will be performed later in the development of this agent. A literature search revealed that ONC201 was inactive in a CYP450 screen. Strong inducers and inhibitors of the cytochrome P450 system should be used with caution.

7 STUDY PROCEDURES/DATA COLLECTION

Note that the hematology, blood chemistry, urinalyses, and procedures below are completed as per standard of care and/or as per the treating physician's discretion unless specified.

- Obtain patient informed consent including patient signature on informed consent form – must be completed prior to dosing
- Medical history, including tumor history, prior treatments, history of other disease processes (active or resolved), concomitant illnesses, and demographics. In addition, provide imaging assessments from initial diagnosis, surgery planning, post-surgical, post chemoradiation, scheduled and unscheduled MRIs.
- Disease signs and symptoms
- Vital signs
- Height
- Weight
- Physical exam
- Performance status (KPS or Lansky; Appendix B)
- Hematology, blood chemistry, coagulation, urinalysis
- Concomitant medications
- Clinical imaging
- Patient reported outcomes
- Corticosteroid use

Any archival tumor tissue slides obtained can be sent to Oncoceutics:

Oncoceutics. Inc.
Attention: Clinical Operations
3675 Market Street, Suite 200
Philadelphia, PA 19104
(clinicaloperations@oncoceutics.com).

7.1 Screening and Enrollment

In order to begin the patient registration process, the site must obtain a slot for the candidate patient from Oncoceutics. At the time of receipt of the signed consent form, Oncoceutics medical monitor must be notified via email to initiate eligibility review. The study staff must include de-identified patient source documentation, the completed New Patient Registration Form (provided by Oncoceutics) and a tentative therapy start date.

Registration approval will be valid for 7-business days from receipt of approval. If the potential patient is not treated within those 7 business days, a new request must be submitted to determine eligibility.

A patient identifier will be assigned at the time of approval. Screening and eligibility MUST be entered into Redcap EDC within 7-business days of screening visit.

7.2 Tumor Specimens

If available, archival tumor tissue samples will be obtained at the time of enrollment for the patient enrolled in this study to assess predictive biomarkers, including histone H3 mutation and expression of DRD2 and DRD5. A minimum of five (5) FFPE archival tumor tissue slides are requested. If multiple samples are available, tissue from the most recent resection/biopsy is requested. The slides should be labeled as “ONC018-name of site-patient’s initials”.

7.3 Patient Withdrawal

The subject may withdraw at any point.

8 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the ONC201, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples

of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the use of ONC201 product within the follow-up period specified by the protocol, from overdose (whether accidental or intentional), from abuse and from withdrawal. Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event.

All adverse events will be recorded from the time the date of initiation of study therapy through 30 days following cessation of treatment and at each examination. Serious Adverse Events will be followed through 90 days following cessation of treatment. Both Adverse events and Serious Adverse Events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

All Adverse Events regardless of seriousness or relationship to the Investigational Product will be recorded in the Case Report Forms. Serious Adverse Events should be reported per the requirements described in Section 7.1.

8.1 Reporting of Serious Adverse Events

Serious Adverse Events: A serious adverse event is any adverse event occurring at any dose or during any use of ONC201 that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- The subject becomes pregnant. If subject becomes pregnant, the investigator must immediately (within 24 hours of awareness of the pregnancy) notify the Sponsor or designee of this event.
- Is another important medical event

Progression of the cancer under study is not considered an adverse event.

Inpatient hospitalization for events due to progression of the cancer will not be considered a serious adverse event.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of initiation of therapy through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to ONC201, must be reported within 24 hours to Oncoceutics.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to ONC201 that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to Oncoceutics.

Investigators **must** report to Oncoceutics any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of treatment on the SAE form provided by Oncoceutics.

SAE reports and any other relevant safety information are to be forwarded to the pharmacovigilance@oncoceutics.com and the Oncoceutics facsimile number within 24 hours of learning of its occurrence: 1-844-245-7650

Oncoceutics will submit all required SAE Reports and Annual Progress Reports to the FDA as required by FDA or other local regulators.

Investigators **must** report SAEs to the local IRB following local IRB reporting requirements.

All subjects with serious adverse events must be followed up for outcome until resolution of the SAE.

8.2 Expected Toxicities

ONC201 is being evaluated in multiple on-going clinical trials that are summarized in the Clinical Investigator's Brochure, along with the safety experience. As of June 21, 2018, 204 patients have been treated with ONC201: 93 patients were male and 111 were female. The age ranged from 3 to 91 years, (median: 61 years; mean 57.9 years). Sixty-three patients received ONC201 on a Q3W schedule, 137 patients received ONC201 on a Q1W schedule and 4 patients received ONC201 on a BIW schedule. The median number of doses administered per patient was 5 (range: 1-50): median 2 (range: 1-31) on a Q3W schedule, median 6 (range: 1-50) on a Q1W schedule and median 6 (range: 5-12) on a BIW schedule. Doses that were administered ranged from 125 mg to 625 mg. A total of 142 patients received 625 mg of ONC201 (the adult RP2D). The other 62 patients received doses of ONC201 less than 625 mg ranging from 125 mg to 500 mg

There have been no drug-related DLTs across the various clinical trials and administration schedules with dose levels ranging from 125 mg to 625 mg. No study drug discontinuations due to toxicities were reported. Only 1 dose reduction (625mg to 500mg) occurred in 1 patient with a Grade 3 neutropenia assessed by the PI as possibly related to ONC201. However, upon re-challenge neutropenia did not recur.

Some patients who received ONC201 have experienced mild or moderate adverse events that were attributed as possibly related to ONC201:

- fatigue,
- abdominal pain,
- fever,
- nausea,
- vomiting,
- anorexia,
- weakness,
- elevated serum amylase,
- neutropenia,
- bone pain,
- generalized weakness,
- allergic reaction, and
- ataxia.

The clinical trial that has enrolled the largest number of high grade glioma patients is NCT02525692 entitled “Oral ONC201 in Adult Recurrent Glioblastoma and H3 K27M-mutant Glioma.” The safety information for this trial is provided in Section 1.3.1.

Side effects seen in animals at exaggerated doses included the following:

- Nausea
- Salivation
- Vomiting
- Abnormal breathing
- Twitching
- Abnormal walking or standing
- Death

For further information related to preclinical and clinical safety experience with ONC201, including expected adverse events, please refer to the Investigator's Brochure.

8.3 Adverse Event Characteristics

Descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

- **Attribution** of the AE:
- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

9 ASSESSMENTS

9.1 Definitions

Safety assessment will be performed using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Objective response assessments will be performed with RANO criteria for patients who have measurable disease by this criteria. Only those patients who have received at least one dose of ONC201 and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

9.1.1 Disease Parameters

Measurable Disease

Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Non-Measurable Evaluable Disease

Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1cm.

9.1.2 Response/Progression Categories

For the purposes of this study, patients should be reevaluated for response approximately every 8 weeks of therapy. In addition to baseline scan(s), confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

The modified RANO Response Criteria to be used in this study are summarized below. If changes in the primary field lesions lead to assessment of progressive disease, this assessment should be confirmed 4 weeks after initial diagnosis.

Complete response (CR). All of the following criteria must be met:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.
b) No new lesions.
c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d) Participants must be on no steroids or on physiologic replacement doses only.
e) Stable or improved non-enhancing (T2/FLAIR) lesions.
f) Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

Partial response (PR). All of the following criteria must be met:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan at least 4 weeks later, this scan will be considered only stable disease.
b) No progression of non-measurable disease.
c) No new lesions.
d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g) Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Progressive disease (PD). Any of the following criterion must be met:

a) > 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids.
b) Any new enhancing measurable lesion.
c) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
d) Failure to return for evaluation due to death or deteriorating condition.

Stable disease (SD). All of the following criteria must be met:

a) Does not qualify for CR, PR, or progression.
b) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c) Stable clinically.

Unknown response status. Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

9.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

9.1.4 Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI at least four weeks later, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best “response.”

9.2 Safety Evaluations

Safety assessments include collection of AEs, SAEs, and safety laboratory will be part of standard of care as per the treating physician’s discretion.

9.3 Patient Reported Outcomes

At the beginning of each clinic visit (e.g. every 28 days) patients will complete the MDASI questionnaire (Appendix A). Patients under 18 years of age do not complete the MDASI..

9.4 Duration of Follow-up

Patients will be followed post-treatment until death, withdrawal of permission to record at least survival data, or subject is lost to follow-up every 30 days (±7 days) after coming off study. Patients or their caregivers will be contacted every 30 days to assess for survival status. Contact may be performed by a site visit, telephone contact, e-mail, or mail. The date of death and date of last contact should be documented if this information is available.

10 DATA HANDLING, IMAGE SUBMISSION AND RECORD KEEPING

Adverse event lists, guidelines, and instructions for reporting adverse events can be found in Section 8.

10.1 Data Reporting

Investigative sites are responsible for completing and submitting data and/or data forms according to the instructions for the selected information management system.

10.2 Submission of Images

Each contrast-enhanced MRI (or CT if MRI is contraindicated) must be submitted for sponsor review. This includes: Baseline scan, disease assessment scans performed every 8 weeks (+/- 7 days), and End of Treatment scan done 30 +/- 7 days post last dose.

The complete MR imaging data sets must be submitted to Oncoceutics Inc. in digital DICOM format within 14 days (+/- 7 days) from each MR acquisition.

Each submission should be de-identified, labeled with the patient study ID number, the time point of the scan (e.g. Baseline, Week 8, etc.), and the industry protocol number. To submit you can use any of these methods:

1) **FTP Transfer:** Coordinate with Oncoceutics (clinicaloperations@oncoceutics.com) to set up FTP transmission of images.

2) **Shipment/Mail:** If the above electronic data transfer cannot be achieved, the de-identified images can be burned to a CD in DICOM format and labeled with the patient study ID number, the time point of the scan (e.g. Baseline, Week 8, etc.), the date of the scan, and the industry protocol number listed on the CD cover and mailed to Oncoceutics Inc. via FedEx Standard overnight at:

   Oncoceutics Inc.
   3675 Market Street, Suite 200
   ATTN: Clinical Development
   Philadelphia, PA 19104
   Telephone: 215-966-6115

10.3 Data Collection

10.3.1 Data Collection Forms

Qualified clinical trial study monitors that represent Oncoceutics may conduct remote and on-site monitoring.

Case Report Forms will be completed in a timely manner. Case Report Form completion may be formally delegated to other study personnel listed in the delegation of authority (DOA) form and signed by the PI.

The following steps will be taken to ensure accurate, consistent, complete and reliable data:

1. The Sponsor or designee will conduct an initiation meeting remotely prior to the start of the study. The study protocol, procedures and CRFs will be reviewed in detail and the study personnel will be trained, if needed, to carry out the procedures defined in the protocol.
2. The Investigator will store the study-related regulatory and study site documentation (e.g. study logs and forms) in a Study Site Binder.
3. All written study documentation entries must be made in blue or black ink. The investigator must review all entries for completeness and accuracy. When changes or corrections are made on any study documentation, the person making the change must draw a single line through the error, then initial and date the correction.
4. Periodic monitoring visits will be conducted on a regular basis by the Sponsor or designee in order to verify the accuracy of data entered on each CRF against the raw data from source documents at the site. Items needing correction/clarification will be identified and brought to the attention of the study site personnel and Principal Investigator, and corrections will be made as appropriate.
5. The CRF will then be sent to the Sponsor or designee for final review and data management. The study database will be validated using appropriate validation processes
6. The Sponsor or designee may perform a regulatory audit of the study site, and may include a complete review of the overall study conduct, regulatory documentation, and selected subject CRFs and source documents.

10.3.2 Registration and Eligibility

Patient eligibility will be confirmed by the investigator after discussing with Oncoceutics. The investigator is responsible for enrolling only those patients who have met protocol eligibility criteria.

10.3.3 Patient Consent Form

Informed consent must be obtained before protocol-specified procedures or interventions are carried out. The investigator will explain the nature of the study and will

inform the subject that participation is voluntary and that they can withdraw at any time. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records.

The consent form must be approved by the IRB and be acceptable to the Sponsor. Consent forms must be written so as to be understood by the prospective subject. The Informed Consent should be translated and certified into the local language of the respondent, as deemed necessary. Informed consent will be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and by the person who conducted the informed consentdiscussion.

The signature confirms the consent is based on information that has been understood. Each signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the Sponsor or its designee. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.

10.3.4 Site Monitoring

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor and duly authorized representative of any entity providing support for thisstudy.

Contractors of the Sponsor will conduct routine monitoring or audit activities for this study. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current FDA Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

11 ANALYSIS CONSIDERATIONS

Descriptive statistics will be provided for selected demographic, safety, and efficacy endpoints. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received ONC201, including serious adverse events (SAEs). Other safety endpoints include laboratory safety assessments, KPS status, vital signs and physical examinations. Efficacy analyses will include progression-free survival by RANO, overall response rate by RANO, duration of response by RANO, overall survival, changes in corticosteroid use, and patient-reported outcomes by MDASI.

Analyses will be conducted for all patients and separately for cohorts categorized by: age (<18 or ≥18 years of age), H3 K27M mutation, primary tumor location (e.g. thalamus, pons, spinal cord), disease status (e.g. first recurrence, second recurrence, not yet recurrent). Descriptive

statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages

12 ETHICS

Institutional Review Board (IRB)
The investigator is responsible for keeping their local IRB informed of the progress with study renewal at least once a year. The investigator must also keep the local IRB informed of any significant adverse events, per local institutional guidelines.

Records Retention: FDA regulations (21 CFR 312.62) require clinical investigators to retain all study- related documentation, including source document and CRFs, long enough to allow the sponsor to use the data to support marketing applications. All records must be maintained for:

- Two years after the FDA approved the marketing application, or
- Two years after the FDA disapproves the application for the indicationbeing studied, or
- Two years after the FDA is notified by the sponsor of the discontinuationof this study and that an application will not be submitted.

For all studies, including studies with FDA-IND exemption, the Investigator/Institution/Sponsor will take measures to prevent accidental or premature destruction of study documents. For such studies conducted under IND exemption, records will be retained for a minimum of seven (7) years past official study termination.

12.1 Ethical Conduct of the Protocol
This protocol will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor and duly authorized representative of any entity providing support for this protocol. Contractors of the Sponsor will conduct routine monitoring or audit activities for this study. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current FDA Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

12.2 Patient Information and Consent
All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures. High standards of confidentiality and protection of patient personal data.

The informed consent form must be approved by the IRB and must be in compliance with ICH

GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB before use. The investigator will retain the original of each patient's signed consent form.

12.3 Publication Policy

It is the intention of Oncoceutics to publish the results of this study in their entirety within a reasonable period of time following conclusion of the trial. The Sponsor will determine when and where data will be first disclosed.

All information generated from this study is the proprietary property of Oncoceutics. Oncoceutics reserves the right, among other, things, to:

- Modify or amend study material to ensure that no confidential or proprietary information is disclosed.
- Ensure that the reported data are factually correct.
- Utilize the information generated from or as a result of this study in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company.
- Modify the publication or disclosure or delay it a sufficient time to allow Oncoceutics to seek patent protenction of any invention contained therein.

13 DISCONTINUATION CRITERIA

Premature termination of this clinical protocol may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Oncoceutics. In addition, Oncoceutics retains the right to discontinue development of ONC201 at any time.

14 REFERENCES

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APPENDIX A

MD ANDERSON SYMPTOM INVENTORY - BRAIN TUMOR (MDASI - BT)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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MDASI-BT - 2006

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

MDASI-BT - 2006

APPENDIX B: KARNOFSKY AND LANSKY PERFORMANCE STATUS CRITERIA

	Karnofsky Scale	Lansky Scale
100	Normal, no complaints, no evidence of disease	Fully active
90	Able to carry on normal activity	Minor restriction in physically strenuous play
80	Normal activity with effort	Restricted in strenuous play, tires more easily, otherwise active
70	Cares for self, unable to carry on normal activity or to do active work	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	Considerable assistance required for any active play, fully able to engage in quiet play
40	Disabled, requires special care and assistance	Able to initiate quite activities
30	**30** Severely disabled, hospitalization indicated, although death not imminent	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	Completely disabled, not even passive play