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Version 12	10/1/18
Version 13	9/16/19
Version 14	6/3/21

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1. OBJECTIVES

The primary objective of this phase II trial is to determine the efficacy of oral ONC201, an oral small molecule DRD2 antagonist that induces the integrated stress response to inactivate Akt and ERK signaling and induce the pro-apoptotic TRAIL pathway in adults with adult recurrent gliomas. Secondary objectives include assessment of intratumoral drug concentrations, safety, overall radiographic response (ORR), ORR duration, overall survival (OS), and progression-free survival (PFS) and correlation with serum and tumor tissue biomarkers.

1.1 Study Design

This is a Phase II multi-center clinical trial with six arms and appropriate stopping rules for poor efficacy.

All subjects in Arm A will receive oral ONC201 every 3 weeks and all subjects in Arm B, C, D, E, and F will receive oral ONC201 every 1 week.

Arm A, B, D, and F will enroll 16-30 evaluable patients each. Arm C will enroll 6 patients who have sufficient resected tumor tissue for correlative studies. Arm E will enroll 12 patients who have sufficient resected tumor tissue for correlative studies. All subjects in Arm C and E will have surgical resection of their tumor 1 day after the second (or more) dose of ONC201.

All subjects will remain on study treatment until progressive disease, unacceptable toxicity, or withdrawal of consent.

All patients will undergo clinical evaluation after each cycle (3 weeks). Neuroimaging studies (contrast-enhanced brain MRI or CT for patients unable to undergo MRI) will be performed at baseline, at 8 weeks from treatment initiation, and then every 8 weeks thereafter.

1.2 Primary Objectives

To evaluate the anti-tumor activity of ONC201 among patients with recurrent glioblastoma or recurrent WHO Grade IV gliomas when treated with ONC201 as assessed by the 6-month progression-free survival (PFS6) rate using the Response Assessment in Neuro-Oncology (RANO) criteria, for high-grade glioma (HGG).

1.3 Secondary Objectives

- Assess the intratumoral concentration of ONC201 in glioma biopsies.
- Estimate the Overall Survival (OS).
- Estimate the Overall PFS
- Estimate the Overall Radiographic Response (ORR) rate based on RANO-HGG and RANO for low-grade glioma (RANO-LGG) criteria.
- Estimate the ORR duration.

- Correlate clinical outcome with serum and archival tumor tissue biomarkers.
- Assess the safety, toxicities, and tolerability of ONC201 in adults with recurrent HGG.

1.4 Intratumoral Correlatives

- To determine the intratumoral concentration of ONC201 achieved in patients treated with ONC201
- To characterize the pharmacodynamic effects of ONC201 on tumor through IHC analysis of ATF4, CHOP, and DR5 on resected tumors of patients exposed to ONC201

1.5 Endpoints

-Efficacy

- Response by RANO-HGG
- Response by RANO-LGG
- Duration of Response by either RANO-HGG or RANO-LGG
- Progression-free survival by RANO-HGG or RANO-LGG
- Overall survival

-Safety

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

-Other

- Quality of Life (MDASI-BT)
- NANO

2. BACKGROUND

2.1 Study Disease

In 2014, there were over 23,300 new cases of cancer involving the brain and nervous system and over 14,000 deaths (Siegel 2014). GBM is the most common and lethal primary malignancy of the central nervous system (CNS) and occurs for over 15% of all brain cancers (Patel 2014). Despite standard of care therapies which include surgical resection, radiation and chemotherapies, the 5-year survival rate for GBM remains at <10% (Stupp 2009). Thus, GBM is an obvious unmet clinical need with dismal survival and limited treatment options that offer meaningful survival benefit. Disease recurrence is common and occurs within months of the completion of first line treatment. The choice of therapy after recurrence is limited. In a phase II study, patients treated with bevacizumab for recurrent disease achieved a 48% PFS-6 (Friedman 2009).

Unfortunately, the PFS-6 observed in studies of bevacizumab did not confer a survival advantage (Wick 2017). Large meta-analyses of clinical trials evaluating efficacy of salvage therapeutics (excluding bevacizumab) consistently reported PFS-6 rates of 9-11% (Ballman 2007; Lamborn 2008; Wu 2010). Therefore, GBM is a difficult-to-treat disease with a large unmet need for innovative, safe, and effective therapies useful in recurrent GBM.

2.2 IND Agent

ONC201 is a first-in-class small molecule with consistent antitumor activity in difficult-to-treat cancers as demonstrated using in vitro, ex vivo, and in vivo models. Favorable attributes of ONC201 observed in preclinical models include antitumor efficacy with infrequent administration, broad-spectrum activity independent of mutations or tumor type, orally active, high safety margins, synergistic activity with many approved therapies, highly stable, highly water soluble, and ability to penetrate the blood-brain barrier. The mechanism of action of ONC201 appears to involve the activation of the integrated stress response (ISR) that causes a downstream inactivation Akt and ERK signaling as well as induction of the pro-apoptotic TRAIL pathway. The efficacy of ONC201 has been demonstrated in numerous solid and liquid tumor cell lines and patient samples that are refractory to chemotherapy and targeted therapies. Importantly, ONC201 is effective in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that result in resistance to chemotherapy and targeted therapies.

- Preclinical Efficacy and Tolerability

ONC201 induces cell death in a broad spectrum of tumor types harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that result in resistance to chemotherapies and targeted agents. ONC201 induces caspase-mediated apoptosis in cancer cell lines and exhibits broad-spectrum cytotoxicity in vitro. ONC201 exhibits promising anticancer activity that has been demonstrated in multiple malignancies in preclinical models that include subcutaneous, orthotopic, and transgenic models in addition to a large body of in vitro data that demonstrate its cytotoxic effects and its mechanism of action. ONC201 displays single agent anti-tumor effects (Figure 2.1) in subcutaneous and orthotopic colon cancer, subcutaneous triple negative breast cancer, subcutaneous non-small cell lung cancer, subcutaneous and orthotopic intracranial glioblastoma, and immunocompetent lymphoma transgenic mouse models. ONC201 also cooperates extensively with paclitaxel, docetaxel, and bevacizumab. We have chosen to target GBM for ONC201 development given the wealth of positive preclinical information that was generated with the study drug.

Preclinical efficacy studies revealed that ONC201 has peak efficacy when administered at 25 mg/kg orally once every two weeks. Administering doses more frequent than every 2 weeks or at doses higher than 25 mg/kg did not yield additional efficacy. To begin to estimate the safety margin of ONC201 in vivo, exploratory exaggerated dosing studies were conducted in mice. ONC201 was administered IP to cohorts of mice as a single dose either as an IP bolus or fractionated IP dose. The single bolus dose was well tolerated up

to 220 mg/kg. At 250 mg/kg, single rapidly administered IP doses of ONC201 caused labored breathing, dyspnea, and death. A dose of 250 mg/kg ONC201 administered IP and divided into four equivalent doses was well-tolerated. Preclinical efficacy of ONC201 in mice was achieved at doses as low as 12.5 mg/kg with maximal efficacy observed in at least one model at 25 mg/kg. Administering ONC201 twice a week in nude mice at 25 mg/kg caused a mild reversible skin rash following two weeks of administration that was not observed with weekly administration.

In addition to potent in vitro activity, ONC201 shrinks temozolomide-resistant GBM xenografts (Figure 2.2A) and prolongs the survival of mice with orthotopic xenografts as a single agent and in combination with bevacizumab (Figure 2.2B). Corroborating observations by other investigators have demonstrated the compelling single agent efficacy of ONC201 in radio- and chemo-resistant GBM cell lines. Other studies have demonstrated highly potent cytotoxic activity with ONC201 in three-dimensional neurosphere cultures of newly diagnosed and recurrent GBM patient samples.

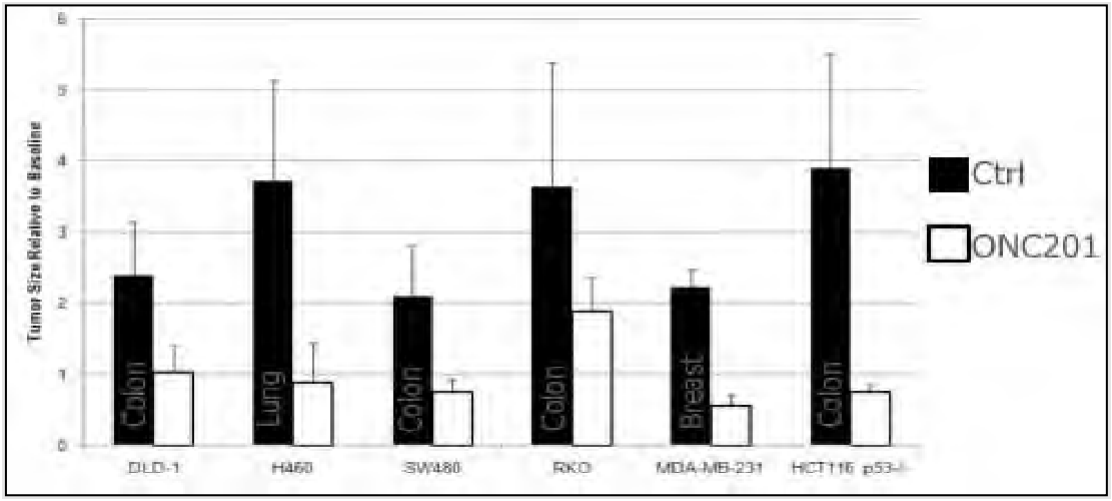


Figure 2.1 ONC201 antitumor activity in subcutaneous xenografts. Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and relative to the tumor size on the day of administration.

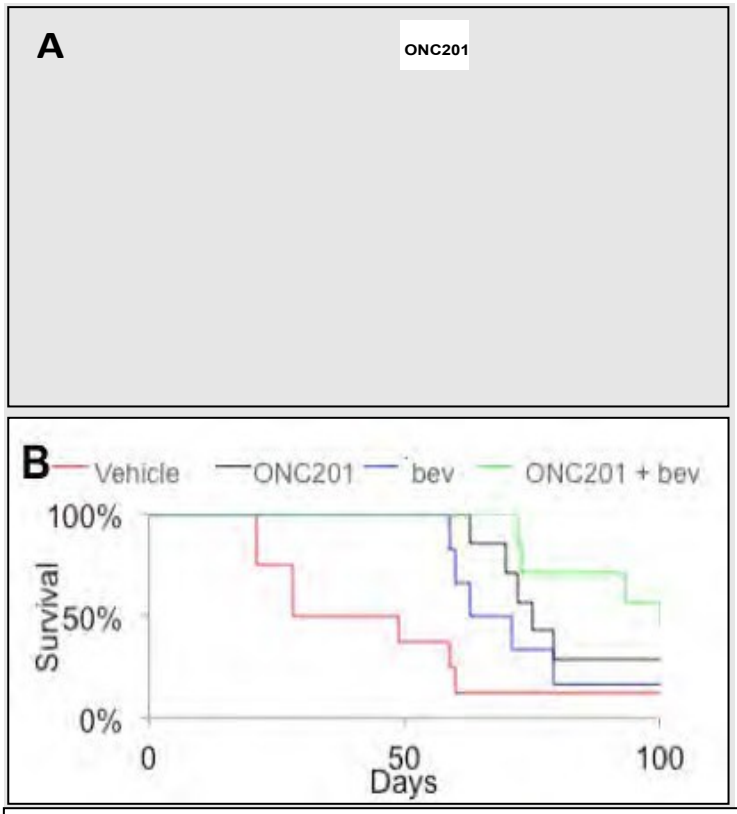


Figure 2.2 (A) Relative tumor size in a subcutaneous xenograft of T98G in mice treated with a single dose of vehicle, ONC201 (30 mg/kg, orally), or bevacizumab (10 mg/kg, iv) (n = 8). (B) Survival of mice harboring SF767 intracranial tumors with a single oral dose of vehicle (n = 8), ONC201 (25 mg/kg, n = 7), bevacizumab (bev) (10 mg/kg, iv, n = 6), or ONC201and bevacizumab (n = 7) at 2 weeks after implantation.

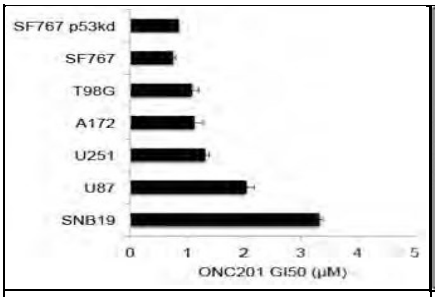


Figure 2.3 GI50 GBM cell lines at 72 hours after treatment with ONC201 or DMSO (n = 3).

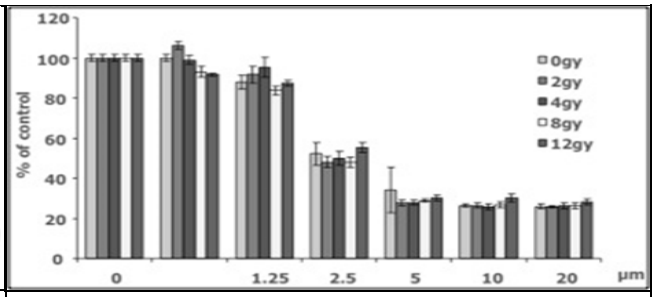


Figure 2.4 T98G TMZ-resistant and radio-resistant GBM cells following treatment with ONC201 at indicated concentrations (72 hr).

ONC201 demonstrates p53-independent activity in human GBM cell lines in the low micromolar range (Figure 2.3). ONC201 exerts a strong cytotoxic effect, unlike temozolomide, against tumor cells isolated from a freshly resected GBM with an

oligodendroglial component that was previously resected and irradiated. Observations by external investigators demonstrate the compelling single agent efficacy of ONC201 in radio- and chemo-resistant GBM cell lines (Figure 2.4) and 3D neurosphere cultures (Figure 2.5).

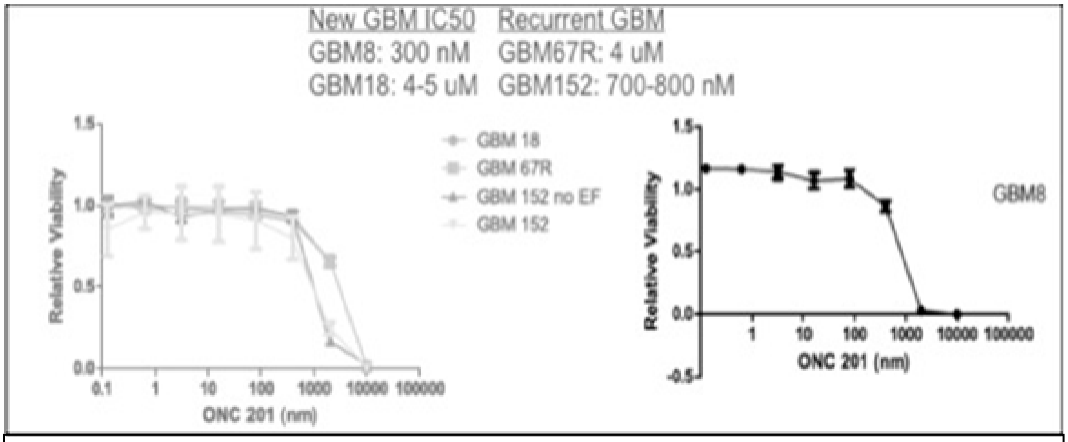


Figure 2.5 ONC201 kills newly diagnosed and recurrent GBM neurospheres. Cell viability of neurosphere GBM cultures following ONC201 treatment (72 hr).

- 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.

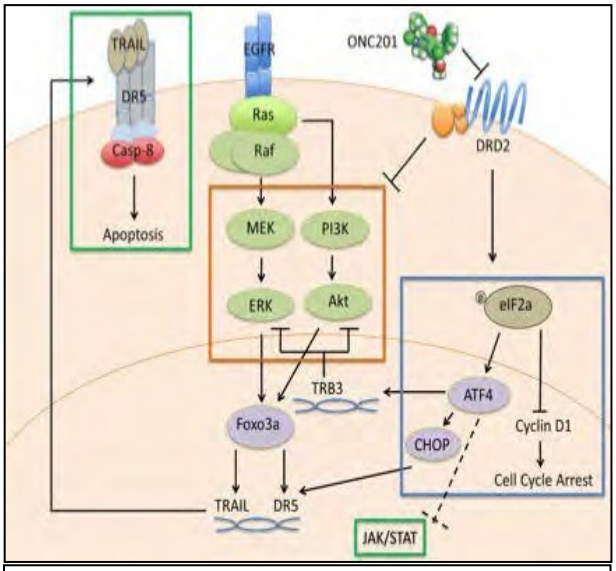


Figure 2.6 Proposed model of ONC201 mechanism of action in tumor cells.

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 2.6). 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. DRD2 antagonism also downregulates Akt and ERK activity to cooperatively induce complementary downstream apoptotic effects. ONC201 may not activate eIF2-alpha through PERK. This distinct mechanism may explain the lack of cross-resistance between ONC201 and other ER stress-inducing agents such as bortezomib. In addition, ONC201 has enhanced antitumor efficacy in combination with bortezomib that may be explained by engaging parallel stimuli that lead to an enhanced activation of the ISR in tumor cells.

- 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 dose 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 at 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 dog GLP 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 rats that 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.

  2.2..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 Cmax. 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.

2.2.3.2 *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, ECG 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 for 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 225 mg/kg. 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.

- Pharmacokinetic Studies

2.2..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 T1/2,e 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. Exposure to ONC201 was similar in male and female dogs with the observation that all mean male Cmax and AUC values were slightly greater than those corresponding female values. Elimination of ONC201 from plasma was similar between the mid and high dose levels; mean T1/2,e ranged from 4.6 to 7.8 hours. Mean T1/2,e 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.

2.2.4.2 *Pharmacokinetic Studies in Humans*

In a phase I dose escalation clinical trial of ONC201 in advanced solid tumors, the pharmacokinetics of single agent ONC201 was determined by LC-MS-MS analysis of plasma collected in the first cycle of therapy within 21 days of drug administration (Fig 2.7; Table 2.1). Trends of increasing exposure with dose were consistent with dose proportionality. Patients receiving 625mg ONC201 exhibited a mean half-life of 11.3 hours and achieved a Cmax of 3.6 ug/mL (~9.3 uM), which occurred at 1.8 hours following administration (Tmax). The mean volume of distribution was 369 L, consistent with a large distributive volume.

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.

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.

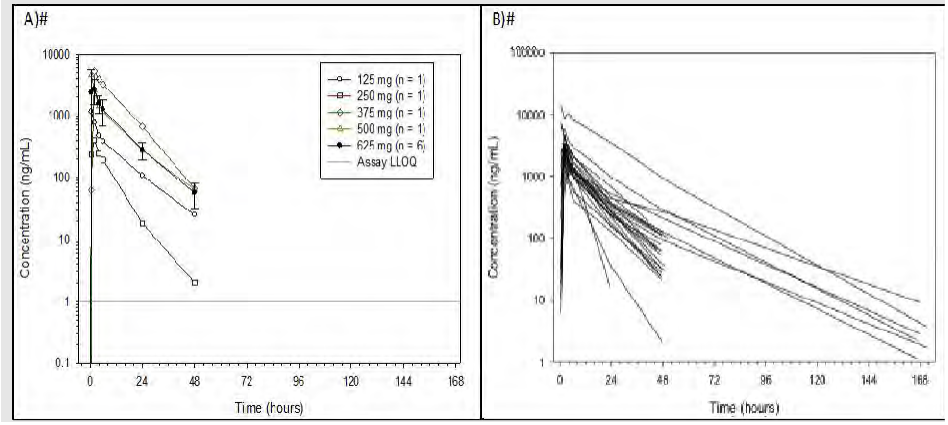


Figure 2.7: Mean ONC201 plasma concentrations versus time following the first dose of ONC201. Concentrations are shown as (A) A mean for each dose cohort, or (B) for individuals treated at 625 mg.

Table 2.1 ONC201 pharmacokinetic parameters determined in patients receiving 625 mg ONC201 (n=24).

	C_{max} (ug/mL)	T_{max} (h)	T_{lag} (h)	AUC_{last} (h.ug/mL)	λ_z (h^{-1})	$t_{1/2}$ (h)	AUC (h.ng/mL)	V_z/F (L)	CL/F (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

2.3 Clinical Studies

*****Refer to the current version of the IB for more up-to-date information on clinical safety and study progress.*****

The clinical safety of ONC201 has been evaluated in a phase I clinical trial. The design was an open-label, dose-escalation phase I trial of single agent ONC201 in patients with advanced, refractory tumors who had exhausted or refused standard treatment options for their respective indications. The primary objective of this study was to determine the recommended phase II dose (RP2D) of ONC201 administered orally in patients with advanced cancers, as well as to evaluate the safety and tolerability of the drug. Secondary objectives included pharmacokinetics and pharmacodynamics evaluation of ONC201 and preliminary assessment of anti-tumor efficacy.

An accelerated dose escalation design was employed to reduce the number of patients treated at potentially sub-therapeutic dose and to accelerate the determination of the recommended phase II dose. Ten evaluable (aged 47-80 years) received oral ONC201

once every 3 weeks at five dose levels ranging from 125 to 625 mg. The study design included only one patient per cohort until any patient experiences a grade 2 adverse event during the first cycle of treatment, defined as 21 days. Five dose levels (125 mg, 250 mg, 375 mg, 500 mg, 625 mg) were selected for the study. Enrollment at each subsequent dose level required that all patients enrolled at the prior dose level completed Cycle 1 dosing and were evaluated 21 days later to assess safety.

On average, patients received 3.1 doses of ONC201. Nine out of ten patients completed at least 2 cycles, 4 patients completed at least four cycles, and one patient received > 6 cycles. 625 mg was the highest dose administered and was determined to be the RP2D that surpassed the absorption saturation threshold by two dose levels. The only adverse event during the dose escalation phase that was possibly attributed to ONC201 was a low grade fever. No drug-related toxicities Grade >1 were observed in any patients in this study. Explorative laboratory studies and physical exams did not reveal any drug-related abnormalities. Similarly, cardiovascular assessments revealed no drug-related effects. Three MedWatch reports were filed with the FDA that reported events that were not attributed to the study drug.

Clinical and laboratory results indicated that the drug possessed biologically activity in the treated patients. Patient #3, a 72 year old with advanced clear cell endometrial (uterine) cancer had a mixed objective response with >50% decrease in lymphadenopathy (10/11 afflicted lymph nodes responded) after 2 doses. Patient #4, a 62-year-old male with renal cancer and bone metastasis with debilitating pain in the clavicle experienced relief from his clavicular pain. Patient #6, a 69-year-old patient with prostate adenocarcinoma, has received 7 doses of ONC201 and has stable disease. Patient #8, a 71-year old colon cancer patient had stable disease for at least 12 weeks with 4 doses of ONC201.

A 47-year-old male with appendiceal cancer (patient #2) had CA27.29 tumor biomarker of 30 units that was in the abnormal range, which decreased to 20 units (normal range) after 4 doses of ONC201. Given the heterogeneity of the tumor types in the enrolled patients, no widely used biomarker was available to uniformly assay all patient samples. Since most solid tumors express cytokeratin-18, the serum M30 assay was selected to detect a caspase-cleaved form of cytokeratin-18 that occurs during apoptosis. Clinical studies have demonstrated the M30 assay to be predictive of clinical response (Demiray 2006) in solid tumors. Induction of the M30 assay for apoptosis was noted in 67% of patients treated at the RP2D with a range of 1.25- to 4-fold increase.

An expansion phase of this Phase I trial with ONC201 enrolled 18 additional patients with advanced solid tumors to confirm the tolerability of the 625mg ONC201 RP2D. The only adverse events among the 18 patients enrolled in the expansion phase that were attributed as possibly-related to ONC201 were: nausea (1 patient), emesis (2 patients), and increased level of serum amylase (2 patients). All of these adverse events were Grade 1 and reversed rapidly. Laboratory studies and physical exams did not reveal any drug-related abnormalities. Similarly, cardiovascular assessments revealed no drug-related effects.

Another arm of this study has been opened to evaluate weekly dosing. Three patients have been treated with 375mg ONC201 on a weekly basis and six patients have been treated with 625mg on a weekly basis. There have been no reports to the sponsor of any drug-related adverse events in any of these patients. All three 375mg and six of the 625mg patients have successfully completed the DLT window (21 days). Based on these findings, the recommended administration schedule of ONC201 is 625mg once every week.

A clinical trial is currently being conducted at the MD Anderson Cancer Center investigating the safety of ONC201 in patients with acute leukemias and myelodysplastic syndrome (study #2014-0731; NCT02392572). Thus far, 3 patients have been enrolled in this study that dosed one patient at 125mg once every three weeks, the other patient at 250mg once every three weeks and a third patient at 375mg once every three weeks. There were 3 reported instances of febrile neutropenia, lung infection (pneumonia) and gastrointestinal disorders. None of these were attributed as drug-related by the Investigator.

Study #2014-0632 (NCT02420795) being conducted at the MD Anderson Cancer center, is a 3+3 design dose-escalation design to determine the safety of ONC201 in patients with relapsed/refractory Non-Hodgkin's Lymphoma (NHL). Thus far, 2 patients have been enrolled in this this trial, of ONC201 dosed at 125mg once every three weeks. No adverse events have been reported.

Study #PH-077 (NCT02609230) is a Phase I dose-escalation study of ONC201 in patients with solid tumors and multiple myeloma, being conducted at Fox Chase Cancer Center. Thus far, 5 patients have received ONC201 125mg once every 3 weeks. Patient 1 experienced an SAE that was initially assessed as possibly drug related (progressed from Grade 2 fatigue at baseline to Grade 3 fatigue). The patient had brain metastases at baseline and rapid progression of underlying disease and associated symptoms within 2 weeks of initiating ONC201 treatment. The SAE attribution that triggered the initial report is under reassessment based on the evidence of progressive underlying disease.

Early in this study, ONC006 (NCT02525692), seventeen glioblastoma patients were treated with 625mg ONC201 q3w as part of Arm A. Prior therapy included radiation, surgery, temozolomide, and others except for bevacizumab. Two of 17 patients had methylated MGMT; two of 17 patients had no measurable disease at enrollment due to salvage surgery. PFS6 was 11.8% with one confirmed partial response by RANO. This response occurred in a 22-year-old patient with a secondary glioblastoma possessing a H3.3 K27M mutation. Both lesions regressed, overall by 96% after and the patient remained on study after >18 months. Six of 17 patients stable disease or a partial response as their best overall response by RANO. One patient enrolled after salvage surgery was disease-free after > 10 months and remained on therapy. OS has not been reached with a median follow-up of 38 weeks (range 4-5). ONC201 was very well tolerated with no drug-related SAEs or discontinuation due to toxicity. Two possibly-related AEs occurred: one grade 3 neutropenia that did not recur upon rechallenge and

one grade 2 allergic reaction that was manageable. Plasma PK at 2 hours post-dose was median 2,586 ng/mL (range 1,320-3,660), serum prolactin induction was observed as a surrogate marker of target engagement, and DRD2 was expressed in all evaluated archival tumor specimens.

Following the response in Arm A, preclinical studies of H3 K27M glioma have indicated that tumor cells with this specific mutation are highly responsive to ONC201. Furthermore, a patient in Arm B with recurrent H3 K27M glioma recently exhibited an unconfirmed complete regression of her thalamic lesion on her first 8 week MRI evaluation.

2.4 Rationale

- Rationale for GBM

The first public disclosure of ONC201 is an expired Boehringer Ingelheim patent that described ONC201 (and a series of other unrelated small molecules) as having potential CNS activity, e.g. as an anticonvulsant (Stähle 1971) An in vitro efficacy screen indicated that GBM is more sensitive to ONC201 relative to most other types of solid tumors (Figure 2.7). One of the key features in the selection process that identified ONC201 as an anticancer agent was its ability to penetrate the blood-brain barrier to address tumors residing in the CNS, unlike many available therapies. Ensuing animal studies revealed that ONC201 rapidly traverses the blood-brain barrier, is highly bioactive in the brain, does not appear to be neurotoxic, and is potently cytotoxic to all tested GBM tumors in vitro, ex vivo, and in vivo (Allen 2013b) ONC201 has p53-indepenent activity against GBM cell lines, including those with resistance to chemotherapy and radiotherapy. In addition to cell lines, ONC201 exerts potent anticancer activity in recurrent GBM samples resistant to all standard-of-care therapies.

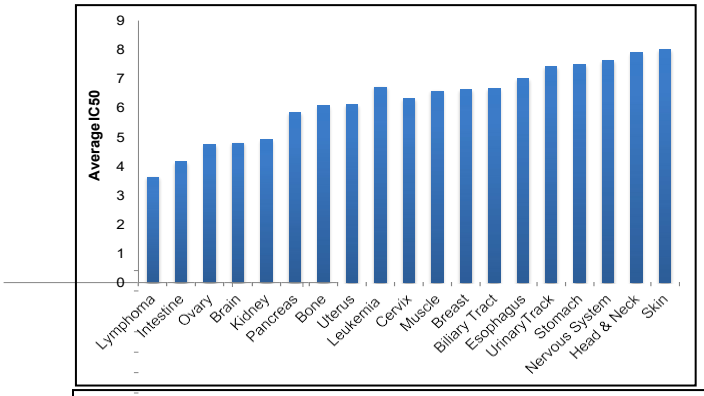


Figure 2.7 In vitro efficacy screen indicating the high sensitivity of GBM (brain cancer) to ONC201.

ONC201 is a first-in-class small molecule that activates the integrated stress response (ISR) in tumors cells that leads to downstream anticancer effects that include inactivation of prosurvival Akt and ERK signaling along with induction and activation of the TRAIL

apoptosis pathway (Allen 2013). The efficacy of ONC201 has been consistently demonstrated in numerous in vitro and in vivo experiments (subcutaneous, orthotopic, and transgenic) by multiple institutions. Despite its strong cytotoxicity in tumor cells, ONC201 does not induce cell death in normal cells. In vivo studies indicate that the safety margin (ratio of therapeutic dose to lowest dose with a mild adverse event) of ONC201 is at least 10-fold in rats and dogs in GLP toxicology studies. The profile of ONC201 is well suited for an oncology product: preclinical efficacy with infrequent administration, broad-spectrum activity independent of mutations or disease type, orally active, compelling safety profile, combines synergistically and safely with many approved therapies, highly active by employing a combination of established anti-tumor/pro-apoptotic pathways, highly stable, water soluble, and penetrates the blood-brain barrier. The high safety and efficacious profile along with its mechanism of action makes ONC201 perfectly suited to address GBM by circumventing limitations of available therapies.

- Rationale for dose schedule

  ONC201 will be administered once every three weeks for Arm A and once every one week for Arm B and Arm C. These infrequent dosing schedules are selected based on the preclinical findings that these schedules are effective and well tolerated in mouse models. This observation is rationalized by the sustained intratumoral activity of the molecule for several days to weeks following a single dose of the drug.

  In preclinical studies, ONC201 acute toxicity is transient and generally resolves within several hours of administration. Preclinical data with ONC201 suggests saturation of efficacy at a human equivalent of 125mg. A dose of 625 mg is expected to exceed the dose (and associated Cmax) with maximal efficacy by 5-fold and thus higher doses may not be explored.

  The frequency of once a week dosing is being evaluated based on the excellent clinical safety and PK observations in the first-in-human study.

2.5 Correlative Studies Background

The novel mechanism of ONC201 involves DRD2 antagonism, which causes downstream induction of integrated stress response and the dual inactivation of Akt and ERK that cause downstream effects, such as TRAIL and DR5 induction, suggests several molecular markers of response in ONC201-treated cancer patients. Immunohistochemical assays for FFPE tumor tissues have been developed for a panel of predictive and pharmacodynamic biomarkers based on mechanism of action and preclinical tumor cell sensitivity studies. Predictive biomarkers for archival specimens include DRD2, DRD5 (an opposing family member), and two proteins that couple to GPCRs called TGM-2 and KSR-1. These and other markers of the status of the molecular mechanism of ONC201 will be assessed on archival tumor tissue samples and serum specimens for all patients.

For Arm C, archival and post-treatment (salvage surgery) tumor tissue will be assayed to

determine intratumoral ONC201 concentrations and molecular markers of response to ONC201. Pharmacodynamic markers for pre- and post-treatment tissue include ATF4, CHOP, and DR5 that are robustly upregulated during activation of the integrated stress response.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

1. For Arms **A, B and C**: Histologically confirmed World Health Organization Grade IV glioblastoma.
   For Arm **D**: Must have a WHO Grade IV glioma and the tumor must harbor a histone H3 K27M mutation detected in a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory by immunohistochemistry or DNA sequencing test on any glioma tumor sample. The H3 K27M mutation is often reported as H3 K28M in gene sequencing assays.
   For Arm **E**: Must have clinical and/or radiographic evidence of a midline glioma (involving the brainstem, thalamus, spinal cord, hypothalamus, basal ganglia, brainstem [non-DIPG], cerebellum, cerebellar peduncle, midline cortex, corpus collosum, pineal region, optic tract, or optic chiasm), and be eligible for salvage surgical resection as deemed by the site Investigator.
   For Arm **F**: Must have a diffuse midline glioma involving the brainstem, thalamus or spinal cord, without the H3 K27M mutation or with unknown H3 mutation status at the time of enrollment.

2. Unequivocal evidence of progressive disease on contrast-enhanced brain CT or MRI as defined by RANO-HGG Criteria, or have documented recurrent glioblastoma or WHO Grade IV glioma on diagnostic biopsy. For Arm E, patients are not required to have evidence of recurrent disease for inclusion.

3. Previous first line therapy with at least radiotherapy and temozolomide. For patients with tumors that exhibit unmethylated MGMT promoter, prior treatment with temozolomide is not required. For Arms D, E, and F, previous first line therapy with at least radiotherapy.

4. For Arm A or D: Any number of recurrences are allowable.
   For Arm B: First recurrence (only) WHO Grade IV glioma. First recurrence is defined as progression following initial therapy (i.e., radiation ± chemotherapy). For participants who had prior therapy with radiation or chemotherapy for a low-grade glioma, the surgical diagnosis of a high-grade glioma will be considered the first recurrence. For patients who did not get additional treatment following surgery and diagnosis of low-grade glioma, surgical diagnosis of high-grade glioma will not be considered the first recurrence. Instead, progression after treatment will be considered first recurrence.
   For Arm C: Patients must have clinical and/or radiographic evidence of first recurrence of glioblastoma and be eligible for salvage surgical resection as deemed by

the site Investigator.
For Arm E: Recurrent disease is not required. Patients must have a midline glioma (defined as a glioma involving the pons, thalamus, spinal cord, hypothalamus, basal ganglia, brainstem [non-DIPG], cerebellum, cerebellar peduncle, midline cortex, corpus collosum, pineal region, optic tract, or optic chiasm), and be eligible for salvage surgical resection as deemed by the site Investigator.

5. 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, then the progressive lesion must be outside of the high-dose radiation target volume or have unequivocal evidence of progressive tumor on a biopsy specimen.

6. From the projected start of scheduled study treatment, the following time periods must have elapsed: 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 antibodies, or 4 weeks (or 5 half-lives, whichever is shorter) from other anti-tumor therapies.

7. All adverse events Grade > 1 related to prior therapies (chemotherapy, radiotherapy, and/or surgery) must be resolved, except for alopecia.

8. Male or Female age ≥16 years.

9. Karnofsky Performance Status (KPS) ≥ 60 (see Appendix A).

10. Adequate organ and marrow function as defined below, all screening labs should be performed within 14 days of treatment initiation:

• leukocytes	≥ 3,000/mcL
• absolute neutrophil count	≥ 1,500/mcL
• platelets	≥ 100,000/mcL
• hemoglobin	> 8.0 g/dL
• total bilirubin	≤ 2.0 x upper limit of normal
• AST (SGOT)/ALT (SGPT)	≤ 2.5 × upper limit of normal
• creatinine	≤ upper limit of normal
OR	
• creatinine clearance	≥60 mL/min/1.73 m2 for patients with creatinine levels above normal.

11. CT or MRI within 14 days prior to start of study drug.

12. Corticosteroid dose must be stable or decreasing for at least 5 days prior to the baseline CT or MRI scan. For Arm B: Corticosteroid dose must be stable or decreasing for at least 2 weeks prior to study entry.

13. The effects of ONC201 on the developing human fetus are unknown. For this reason,

women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Male subjects should agree to use adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of therapy.

14. Archival tissue for evaluation of correlative objectives (if available). Archival tissue is required for Arms B and C.

15. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ONC201 or its excipients.

2. Current or planned participation in a study of an investigational agent or using an investigational device.

3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

4. Active infection requiring systemic therapy.

5. Prior stereotactic radiotherapy, convection enhanced delivery (CED) or brachytherapy must have had a biopsy to confirm radiographic progression is consistent with progressive tumor and not treatment-related necrosis. If the recurrent lesion is outside of any prior high-dose radiation target volume or distant from the prior CED or brachytherapy site, subjects will be considered eligible

6. Pregnant women because ONC201 is novel agent with unknown potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ONC201, breastfeeding should be discontinued if the mother is treated with ONC201.

7. Known HIV-positive test on combination antiretroviral therapy.

8. Known history of cardiac arrhythmias including atrial fibrillation, tachyarrhythmias or bradycardia. Receiving therapeutic agents known to prolong QT interval will be excluded. Patients on sertraline which has the conditional risk of prolonging the QT interval will be allowed on study if they hold sertraline on the day of ONC201 administration. History of CHF, or MI or stroke in the last 3 months will be excluded.

9. Active illicit drug use or diagnosis of alcoholism.

10. For Arms A, B, C, prior bevacizumab for treatment (allowable for Arms D, E, and F).

11. Tumors with known IDH1 (isocitrate dehydrogenase 1) or known IDH2 mutations as determined by immunohistochemistry for the IDH1 R132H variant or by direct sequencing. IDH1/2-mutant gliomas have a markedly longer overall survival rate compared to those with IDH1/2-wildtype glioma (Parsons 2008; Yan 2009), indicating IDH1/2-mutant gliomas have a distinct natural history.

12. Known additional malignancy that is progressing or requires active treatment within 3 years of start of study drug. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

13. Any surgery (not including minor diagnostic procedures such as lymph node biopsy) within 2 weeks of baseline disease assessments; or not fully recovered from any side effects of previous procedures.

14. Concomitant use of moderate to strong CYP3A4/5 inhibitors during the treatment phase of the study and within 72 hours prior to starting study drug administration.

15. Concomitant use of potent CYP3A4/5 inducers, which include enzyme inducing antiepileptic drugs (EIAEDs) (see Appendix B), during the treatment phase of the study and within 2 weeks prior to starting treatment.

16. Planned concurrent use Optune™. Prior use of the device is allowable.

17. For Arm D and F: Evidence of leptomeningeal spread of disease.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

The investigator is responsible for enrolling only those patients who have met all eligibility criteria. The investigator is required to register each patient with the Study sponsor prior to enrollment. After a patient signs the informed consent form, the investigator notifies the medical monitor. The investigator must provide de-identified patient source documentation and a registration form prior to the initiating study treatment. A patient identifier will be assigned at the time of approval. Screening and eligibility MUST be entered into electronic data capture (EDC) within 7-business days of the screening visit.

5. TREATMENT PLAN

5.1 Treatment Regimen

One cycle is defined as three weeks. ONC201 will be provided as an oral capsule at a strength of 125mg per capsule (alternative strengths may be manufactured). For patients enrolled in Arm A, treatment with ONC201 will be administered once every three weeks in the clinic at the RP2D of 625mg.

For patients in Arm B, C, D, E, and F, ONC201 will be administered weekly (i.e., days 1, 8, and 15 of each cycle) at the RP2D of 625mg. For all participants, C1D1 dose will be taken in clinic. All other doses may be taken at home.

For Arm C and E, subjects must be evaluated prior to dosing for the first dose after surgery (i.e. the dose that would occur approximately one week post-surgery). For Arm C and E, ONC201 initiation will be scheduled so that surgical resection will be performed approximately 24 hours after at least the second dose of ONC201 (6 patients for each arm).

If it is not possible to coordinate the timing on the surgery and administration of ONC201 on consecutive days, deviation from this timing is permitted. For Arm C and E, patients will continue weekly dosing one week after surgical resection if the patient is deemed by the treating physician to be sufficiently recovered from surgery; patients requiring a delay of >3 weeks should go off protocol therapy. Arm C and E participants will be required to undergo pretreatment evaluation (to include vitals, physical examination, laboratories), prior to dosing for this day (i.e. if surgery occurs 24 hours after cycle 1 day 8, patients will be required to undergo clinical and laboratory evaluation on cycle 1 day 15). This dose may still be taken at home after the clinical evaluation. Patients in Arm C and E who after surgery are found to have insufficient resected tumor tissue for correlative studies will continue on treatment but will not count towards accrual of Arm C or E.

ONC201 should be taken with a glass of water and consumed over as short a time as possible. Patients 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 an ONC201 treatment must be noted as an adverse event (AE).

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

Hematologic lab values should be re-evaluated on cycle 1 day 1 and need to meet eligibility parameters to start treatment. All patients must sign an informed consent prior to any study-specific procedure. All patients will be screened for Karnofsky performance status (KPS).

For screening, patients will have the following hematologic, serum chemistry, coagulation, urine and pregnancy tests done at the treating institution or in a local lab within 14 days of treatment initiation:

<table>
<tr><td colspan="3">SCREENING FOR ELIGIBILITY</td></tr>
<tr><td>Hematology Panel</td><td>Blood Chemistry Panel</td><td>Others</td></tr>
<tr><td>ANC</td><td>AST (SGOT)</td><td>Pregnancy test</td></tr>
<tr><td>Platelet count</td><td>ALT (SGPT)</td><td>Urine (blood, protein, leukocyte esterase, glucose, creatinine, microscopic examination of the sediment)</td></tr>
<tr><td>Hematocrit</td><td>Creatinine</td><td>Coagulation tests (PT, PTT, and INR)</td></tr>
<tr><td>Hemoglobin</td><td>Total and direct bilirubin</td><td rowspan="9"></td></tr>
<tr><td>RBC count</td><td>Alkaline phosphatase</td></tr>
<tr><td>WBC count with differential</td><td>Calcium</td></tr>
<tr><td rowspan="7"></td><td>LDH</td></tr>
<tr><td>Magnesium
Phosphate</td></tr>
<tr><td>Potassium</td></tr>
<tr><td>Random glucose</td></tr>
<tr><td>Sodium</td></tr>
<tr><td>BUN
Albumin
Total protein</td></tr>
</table>

The evaluations below will be performed within 14 days prior to start of treatment. Screening studies, if performed within 2 weeks prior to start of treatment, are acceptable for use as baseline:

- Patients will undergo complete history including history of concomitant medications, physical examination, measurement of vital signs (pulse, sitting or supine blood pressure, respiratory rate, temperature) and weight, and clinical assessment of KPS. In addition, provide imaging files and assessments from initial diagnosis, surgery planning, post-surgical, post chemoradiation, schedule and unscheduled MRIs.

- For Arms A, B, C and D, pathology report confirming a diagnosis acceptable per eligibility criteria specified for the intended arm. For Arms E and F, radiology or pathology report confirming a diagnosis acceptable per eligibility criteria specified for the intended arm.
- A 12-lead ECG will be performed.
- For Arms D and F, a contrast-enhanced brain MRI and entire spine MRI (or CT if MRI is contraindicated) must be obtained within 14 days of the first dose of study treatment.

5.3 Treatment and Evaluation Cycles

At the beginning of each treatment cycle (i.e., every 3 weeks) patients will also have safety laboratory studies, physical examination, assessment of KPS, and complete the MDASI questionnaire. During discussion of the patient's progress, adverse events and concomitant medications will be collected by targeted questioning.

Patients who remain on study will have tumor response assessments performed at 8 weeks (± 7 days) after initiation of therapy and then every 8 weeks (± 7 days) thereafter.

In addition to reassessment scans, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response (OR). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Patients are to return to the clinic every 3 weeks during the first 6 months on trial. If after 6 months, the patient and the investigator may agree to extend the interval for clinic visits to every 9 weeks (3 cycles). The laboratory assessments must still be performed every three weeks but may be done locally. Brain MRI or CT (for patients who cannot receive MRI scans) will be repeated every 8 weeks, with a 10-day window is allowed after the first 6 cycles.

Unscheduled visits: If a brain surgery or biopsy is scheduled during the active study or within 30 days from the end of treatment date, the investigator may obtain tumor tissue with patient's consent.

5.4 End of Treatment Visit

Following completion of treatment, for patients who discontinue for toxicity or withdrawal, tumor imaging is at the judgment of the investigator, suggested to be no less than every 8-12 weeks in appropriate setting.

If patients come off treatment for progression of disease, intolerance, or patient withdrawal, they will be seen for assessments of efficacy and safety.
Patients will have repeat safety labs, a clinical examination, weight and KPS assessments, and concurrent medications.

If tumor assessments have not been done within the prior 4 weeks, these will be obtained within the next 2 weeks after the End of Treatment Visit.

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring and 30 days (or until start of next line of anticancer therapy) for serious adverse event reporting.

Participants removed from protocol therapy for unacceptable adverse events (Section 7) will be following until resolution or stabilization of the adverse event.

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up.

Subjects will be followed for survival every 30 days after stopping treatment with ONC201.

5.5 General Concomitant Medication and Supportive Care Guidelines

Because the potential for interaction of ONC201 with other concomitantly administered drugs through the cytochrome P450 system is not known, the clinical source documentation will capture the concurrent use of all other drugs, over-the-counter medications, and/or alternative therapies. The Sponsor should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the clinical source documentation.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment will be discontinued for progression of disease, intolerance (defined as NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade 4, Grade 3, or intolerable Grade 2 toxicity that does not return to Grade 1 or baseline after 3 week interruption of treatment or reduction of dose) despite dose modification, or patient withdrawal. A patient who experiences a DLT is able to remain on study at a reduced dose (see section 6), if deemed by the physician to be safe and beneficial for the patient to continue.

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Confirmed radiographic disease progression. Treatment beyond radiographic progression, with prior agreement by the Sponsor's medical representative and investigator, may be allowed if considered in the best interest of the patient. This may include the addition of bevacizumab and/or radiotherapy as clinically indicated

and per local standard practice.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Treatment interruption for more than 3 consecutive weeks due to intolerance despite appropriate dose modification,
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator,
- Global deterioration of health-related symptoms,
- Protocol non-compliance,
- Pregnancy,
- Lost to follow-up, or
- Study termination by Sponsor.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information, then no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.7 Duration of Follow Up

After documented disease progression each subject will be followed by telephone or medical record review for overall survival. When available, subsequent cancer treatment information and disease imaging up to two years after end of treatment visit will be obtained for patients after discontinuing ONC201 treatment.

Participants will be followed up for survival until one of any of the following criteria apply: lost to follow-up, withdrawal of consent, death.

5.8 Criteria for Taking a Participant Off Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the clinical source documentation.

Severe adverse events, availability of new adverse toxicology in animals, and financial difficulties due to withdrawal of funds may result in stopping the trial. An investigator, Sponsor, or IRB may take such actions. If the trial is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-

up will be available. If an investigator terminates the trial, the investigator will inform the Sponsor, subjects, and IRB about the reason for such action. Similarly, if the Sponsor terminates the trial, it will inform the investigators, the IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IRB if it takes such an action.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the clinical source documentation.

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 (Table 6.1) for adverse events that are attributable to study drug. 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 any time during a cycle.

Criteria for disrupting treatment, dose modification, or discontinuation are listed in Table 6.1. 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.

Table 6.1 Dose adjustment rules for Adverse Events (AEs) Attributable to Study Drug. 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 3 weeks, 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.	

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 Sponsor.

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 Sponsor, as long as there has been no significant evidence of disease progression (e.g., by clinical findings, symptoms, tumor markers) during the treatment interruption.

7. 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 in clinical trials or 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 of initiation of study therapy through completion of the safety follow-up period. This period is from the time of discontinuation of ONC201 treatment until 30 days after discontinuation of treatment or until initiation of a new post-discontinuation anticancer treatment, whichever comes first. If a patient initiates a new anticancer treatment within 30 days after discontinuing ONC201, the safety follow-up visit should be conducted prior to the start of that new line of therapy, if possible. Regardless of the end of the safety follow-up period or any new therapies, all SAEs that are deemed at least possibly related to ONC201 should be reported to the Sponsor and followed to resolution.

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 SAEs and AEs related to study treatment or leading to discontinuation should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. 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.

7.1 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;
- Is another important medical event

Progression of the cancer under study is not considered an 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 30 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 the Sponsor.

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 the Sponsor.

SAE reports and any other relevant safety information are to be forwarded to the Sponsor email noted on the Sponsor Contact List.
The Sponsor will submit all required SAE Reports and Annual Progress Reports to the FDA as required by FDA or other local regulators.

All subjects with serious adverse events must be followed up for outcome.

Investigators **must** report to the Sponsor any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last

dose of treatment on the SAE form provided by the Sponsor.

Investigators **should** report SAEs to their governing IRB following their governing-IRB's reporting requirements.

7.2 Expected Toxicities

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

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:**

The 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. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **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.

8. PHARMACEUTICAL INFORMATION

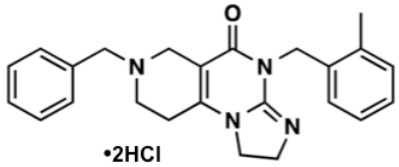
The investigational drug product is a hydroxypropyl methylcellulose (HPMC) capsule filled with ONC201 dihydrochloride salt, intended for oral administration. Each capsule of drug product contains 125mg of anhydrous ONC201 free base (equivalent to 148.8 mg of ONC201.2HCl). ONC201 capsules are manufactured using the following excipients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

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.

Each ONC201 bottle will be labelled in accordance with applicable regulatory requirements and will include the following minimum information:

- Name of study drug and strength
- Sponsor name
- Batch Number
- Storage condition
- Route of administration
- Applicable caution statement according to in-country requirements

8.1 Drug Substance Description

Compound Code(s)	ONC201•2HCl
Alternative Name(s)	ONC201 TIC10 NSC-350625
Chemical Name(s)	7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one 2HCl
Molecular Formula	C24H26N4O (free base) C24H26N4O•2HCl (salt)
Molecular Weight	386.49 (free base) 459.41 (salt)
Molecular Structure	

8.2 Drug Product Description

8.2.1 Form

The investigational drug product is a hydroxypropyl methylcellulose (HPMC) capsule filled with ONC201 dihydrochloride salt, intended for oral administration. Each capsule of drug product contains 125mg of anhydrous ONC201 free base (equivalent to 148.8 mg of ONC201.2HCl). ONC201 capsules are manufactured using the following excipients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

The drug product will be packaged as 10 capsules per bottle. The capsules are filled into a 30cc high-density polyethylene (HDPE) white opaque bottle sealed with a 28 cc child-resistant SecuRx polypropylene (PPE) cap with a heat induction seal.

8.2.2 Storage and Stability

ONC201 should be stored at controlled room temperature (i.e., 15°C to 25°C [59°F to 77°F]), with excursions permitted to 30°C (86°F).

The investigator or qualified designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and must report and

resolve any discrepancies before use of the study drug.

8.3 Drug Product Supply, Administration and Inventory

8.3.1 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.2 Availability

ONC201 is provided by the Sponsor. A sufficient quantity of study supplies will be supplied to the investigator (or qualified designee) at each study center by the Sponsor or Sponsor-authorized depot. Once received at the study center, ONC201 should be stored in accordance with the storage conditions, in a securely locked area, with limited access to authorized site staff.

Only patients enrolled in the study may receive study drug and only authorized site staff may prepare, supply, or administer study drug.

If a subject cannot physically visit a study site, the site may choose to ship the study drug direct to the patient. Upon patient consent and regulatory approval, investigational product may be delivered to his/her designated location (e.g., home, office) via a Chimerix approved direct to patient courier service. Study drug pick up and delivery must be arranged by the study site with the direct to patient courier service . In compliance with data privacy regulations, the vendor has a data privacy system in place to cover any local obligations.

8.3.3 Administration

Patients will receive ONC201 while in the clinic for C1D1. Patients can take medications at home for other dosing. The study drug, ONC201, will be supplied in capsule form for oral dosing.

Study patient will receive a 3-week supply of ONC201 during office visit for the first 6 cycles (not applicable to Arm A, which is closed). After the first 6 cycles, the Investigator can prescribe a supply up to 10-weeks beyond the first 6 cycles considering an allowed 10-day window for repeating MRI every 8 weeks.

Patients should take the dose of ONC201 specified by their physician 2 hours prior or 2 hours following food or a meal. If the patient vomits after taking ONC201, they should not retake the dose. Missed doses will not be made up, if more than 3 days from the intended day of administration.

ONC201 should be taken with a glass of water and consumed over as short a time as

possible. Patients 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.

8.3.4 Accountability

The investigator (or qualified designee) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of the shipment(s) of study drug (date, quantity, and condition), participant dispensing records, and returned or destroyed capsules. Dispensing records will document the dispensing of the study drug to individual participants (including date dispensed, and participant identifier number), the initials of the person(s) dispensing the study drug, and the return and/or disposal of the study drug. All study drug records must be maintained at the site and copies must be submitted to the Sponsor at the end of the study.

8.3.5 Destruction and Return

After verification of the study drug records by the study monitor, all remaining study drug supplies should be destroyed according to directions provided by the Sponsor (or its designee) and/or any applicable site-specific standard operating procedures. If necessary, unused study drug supplies may be returned to the appropriate depot with prior approval from the Sponsor (or its designee). If study drug is approved for onsite destruction by the Sponsor, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacodynamic Studies

As part of this study we will retrieve archived tumor tissue samples at the time of enrollment for subjects enrolled in this study to conduct future correlative assays to measure biomarkers of therapeutic response to ONC201 including molecular markers involved in the mechanism of action of ONC201. The mechanism of action of ONC201 appears to alter the expression or phosphorylation of several proteins involved in cell signaling pathways that govern tumor cell survival and cell death. To assay such changes, serum samples will be obtained for subsequent analysis of pharmacodynamic effects of ONC201.

One tube of blood for serum PD samples will be taken at baseline on Day 1 of Cycle 1 (prior to ONC201 dosing), and again on Day 2 and 8 of Cycle 1, then again at pre-dose on subsequent cycles, and at the follow-up visit at the end of treatment, for correlative studies.

To obtain serum, one (1) tube of 6 mL of peripheral blood will be collected without anticoagulant. The sample will be allowed to clot, and serum will be harvested by iterative centrifugation. Serum will be divided into 2-3 mL aliquots and stored cryogenically. Detailed procedures and supplies are described in the lab manual associated with this protocol.

Archival tumor assessments of cell signaling pathways that are associated with ONC201 will be conducted on tissue obtained from participants. If available, a minimum of 1 formalin-fixed paraffin-embedded (FFPE) archival tumor tissue block (preferred) or a minimum of 10 FFPE unstained sections from most recent pre-registration biopsy/surgery are to be submitted within 60 days of registration.

For patients in Arm C and E, both archival as well as freshly resected tumor tissue will be collected. The tumor may be resected using neuronavigation or intraoperative MRI, enabling resection of enhancing tumor and resection or biopsy of non-enhancing tumor. Surgical resection of the non-enhancing lesions should be performed only in the non-eloquent areas that show FLAIR changes on MRI. Tissue may be collected from both the enhancing core and non-enhancing edge of individual tumors. Tissue should be separated into enhancing and non-enhancing specimens. Tissue will then be divided into four samples. The diameter of tissue will be approximately 0.3 to 0.5 cm for each of the 4 pieces of the tumor that will be preserved. Three will be flash frozen for RNA, DNA, protein, and drug concentration analyses. The fourth sample will be formalin-fixed and paraffin-embedded tissue blocks will be prepared for immunohistochemistry. If possible, a cross section of the resected tissue spanning the tumor and normal margins is requested for the formalin-fixed specimen. The tissue will be assayed for the following markers that have been implicated in the mechanism of action of ONC201 such as DRD2, DRD5, TGM2, KSR1, ATF4, CHOP, pAkt, pERK, TRAIL, and DR5 (Allen 2013a; Ishizawa 2016; Kline 2016).

Please refer to the study laboratory manual for shipping instructions.

9.2 ONC201 Plasma Concentration

For each patient, one (1) EDTA tube of 6 mL of blood will be collected in EDTA tubes at baseline on Day 1 of Cycle 1 (prior to ONC201 dosing), and again 2 hours (± 15 minutes) following the first dose of ONC201, and then not again until the follow-up visit at the end of treatment. All samples will be processed to produce plasma that will be stored cryogenically until analysis. A detailed procedure is provided in the lab manual.

10. STUDY CALENDAR

Study visits and procedures may be scheduled with a ± 3 business day window except for the Screening visit and neuroimaging (contrast-enhanced CT or MRI) (± 7 days). One **Treatment Cycle** is defined as 3 weeks (21 days). One **Evaluation Cycle** is defined as 8 weeks (56 days ± 7 days). ONC201 will be administered every 3 weeks for patients in Arm A and every week for patients in Arm B, C, D, E, and F.

	Screening / Baseline	**CXD1 (All Arms)**	**D2C1 for All Arms**	**D8C1 for All Arms**	**D15C1 for Arms C and E only[10]**	**Unscheduled visit, or brain surgery**	**Evaluation Cycles**	**End of Treatment / Follow-up**
	Within 28 days of Treatment	**(21± 3 days)[14]**					**Every 8 weeks (56 ± 7 days)**	**(30 ±3 days post last dose)**
Medical/RX history, including prior CT/MRI scans[11]	X							
Physical exam, Neurologic exam, KPS, Height, weight[1]	X	X			X	X		X
Vital signs[2]	X	X			X	X		X
12-lead ECG	X	X			X	X		X
Hematology[3]	X	X			X	X		X
Full serum chemistries[3]	X	X			X	X		X
MDASI questionnaire	X	X						X
Coagulation tests	X							X
Pregnancy test[4]	X							X
Disease assessment[5]	X						X	X
Screening brain/spine CT/MRI[10]	X							
AEs[12]		→						
Con-meds		→						
Blood sample for ONC201 plasma concentration		X[7]						X
Fresh tumor tissue[13]					X	X		
Blood sample for PD		X[8]	X[8]	X[8]				X
Disease status and survival[6]								X
Archival tumor tissue	X[9]							

1. Determine if significant weight loss or gain (± 10%). Abbreviated PE on Day 1 of each treatment cycle or as clinically indicated. Neurological assessments will use the NANO scale.
2. Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature prior to treatment on day 1 of each cycle. Vitals will also be required 2 hours after dosing for day 1 of cycles 1 and 2.
3. Obtain and review prior to each dose of ONC201 on Day 1 of each subsequent cycle, or more frequently if clinically indicated.
4. Pregnancy Test – baseline within 7 days of start of treatment and at end of study - urine or serum in women of child-bearing potential. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
5. Neuroimaging (disease assessments) must be taken within 7 days prior to physician visit. Disease assessments will be performed at 8 weeks and then every 8 weeks (± 7 days) thereafter until patients come off study.
6. Every month via telephone for all subjects for 1 year.
7. Obtain blood sample for cycle 1 day 1 only at baseline prior to ONC201 dosing and again at 2 hours (± 15 minutes) post-administration of ONC201.
8. Obtain blood sample for PD pre-dose on day 1 of cycle 1, Day 2, and pre-dose on Day 8 of cycle 1. For cycles 2 and beyond, only pre-dose blood samples on day 1 of each cycle will be collected.
9. Obtain archival tumor tissue (if available) at the time of enrollment, in accordance with the laboratory manual. For Arm C and E, patients must be clinically evaluated prior taking the dose immediately following surgery. Typically surgery will occur 24 hours after the second dose of treatment, meaning that for day 15 of cycle 1 (ie, the dose following surgery), patients will be evaluated prior to taking this dose. Drug may be taken at home after this assessment. However, if surgery is not planned to occur until after the third dose of treatment, subjects will not be required to have an evaluation on day 15 of cycle 1. The dose immediately following surgery would fall on day 1 of cycle 2, a day where all patients are required to come into clinic for clinical and laboratory assessment.
10. Baseline brain MRI, with and without contrast is required within 14 days from C1D1. Brain CT is acceptable for patients who are not able to conduct MRI scans. Entire MRI scans with and without contrast is required for patients to be screened for arms D and F.
11. Provide imaging files and assessments from initial diagnosis, surgery planning, post-surgical, post chemoradiation, scheduled and unscheduled MRIs.
12. The safety follow-up period lasts until 30 days after discontinuation of study treatment or date initiation of a new anticancer therapy after discontinuation of ONC201.
13. Fresh tumor tissue to be collected for both arm C and E from surgery occurring prior to C1D15 (timing may vary depending on surgical schedule and other factors without being considered a protocol deviation). Fresh tumor collection may be obtained from unscheduled brain tumor surgery while patient is on active treatment and until 30 days from last ONC201 dose.
14. If a patient completes 6 cycles the patient may be seen every 8 weeks for routine assessment of physical exam, and AE/concomitant medication assessment.

11. MEASUREMENT OF EFFECT

After signing informed consent patients will undergo screening procedures including baseline radiologic imaging by contrast-enhanced CT scan or MRI within 14 days prior to initiating study drugs.

Patients who remain on study will have tumor assessments performed at 8 weeks (± 1 week) after initiation of therapy and then every 8 weeks (± 1 week) thereafter. In addition to reassessment scans, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response. To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

Efficacy will be assessed by the RANO response criteria as noted below. RANO-HGG and RANO-LGG will be used for each evaluation to assess contrast-enhancing lesions and T2/FLAIR hyper-intense lesions, respectively.

11.1 Definitions

Evaluable for Efficacy and Safety
Patients who have received at least one dose of study drug will be considered evaluable for efficacy and safety. These patients will have response classified according to the definitions stated below.

Evaluable for Intratumoral Concentrations
Patients in Arms C and E must have sufficient tumor tissue from biopsy to permit quantitation of intratumoral concentrations of ONC201 to be considered evaluable for these arms. Patients found to have insufficient tissue may continue treatment, but will be replaced.

Evaluable Non-Target Disease Response
Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease (a+b >10mm), have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for nontarget disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

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

ORR by RANO-HGG is defined as the proportion of subjects in the analysis population who have confirmed complete response (CR) or partial response (PR) using RANO-HGG criteria. Radiographic assessments will be performed by the investigator for the primary endpoint, but may also be separately assessed by blinded independent central review. Duration of response

is defined as time from first RANO-HGG response (only if confirmed) to disease progression in subjects who achieve a PR or better.

ORR by RANO-LGG is defined as the proportion of subjects in the analysis population who have confirmed CR, PR, or minor response (MR) using RANO-LGG criteria determined by the investigator (but may be separately assessed by blinded independent central review). Duration of response is defined as time from first RANO-LGG response (only if confirmed) to disease progression in subjects who achieve a MR or better.

11.2 Disease Parameters

Measurable Disease
Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or 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-measurable 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.

11.3 Response/Progression Categories

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 must be confirmed at least 4 weeks later.

11.3.1 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.

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

11.3.2 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.

11.3.3 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.

11.3.4 Minor Response (MR).

Apply to T2/FLAIR hyper-intense lesions only. All of the following criteria must be met:

a) 25–50% reduction in perpendicular diameters of lesion
b) No new lesions.
c) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
d) Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

11.3.5 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.

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

11.4 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 4 weeks 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.

11.5 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."

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for reporting adverse events can be found in Section 7.

12.1 Data Reporting

Investigative sites are responsible for completing and submitting data and/or data forms according to the user requirements of the EDC system.

12.2 Data Collection

12.2.1 Data Collection Forms

Qualified clinical trial study monitors that represent the Sponsor will complete onsite (or remote) monitoring. the Sponsor will be responsible for all data management and statistical analysis.

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 at the study site 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 to carry out the procedures defined in the protocol.
2. The Investigator will be provided with a Study Site Binder for storing study related regulatory and study site documentation; e.g., study logs and forms.
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.

12.2.2 Registration and Eligibility

At the time of receipt of the signed consent form, the Sponsor 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 the Sponsor) and a tentative therapy start date. Correspondence from the Sponsor for patient registration approval will be granted within 48 hours of receipt of adequate documentation.

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

12.2.3 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 consent discussion. 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, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

12.2.4 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 this trial. 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.

12.2.5 Institutional Review Board Approval

This protocol, the informed consent document, relevant supporting information and all types of patient recruitment and advertisement information must be submitted to the local IRB for review and must be approved before the study is initiated. An amendment to remove a life-threatening situation can by implemented by the Investigator prior to obtaining IRB approval by the site. In such situations, the IRB must be notified immediately and the amendment forwarded to the IRB for their consideration.

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. If this study is conducted under an IND, 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 indication being studied, or
- Two years after the FDA is notified by the sponsor of the discontinuation of trials 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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

Arm A will accrue at least 16 evaluable patients. Arms B, D, and F will accrue 16-30 evaluable patients each. Arms C will accrue 6 evaluable patients who have sufficient resected tumor tissue for correlative studies. Arm E will accrue 12 evaluable patients who have sufficient resected tumor tissue for correlative studies. Patients in Arm C or E who after surgery are found to have insufficient resected tumor tissue for correlative studies will continue on treatment but will not count towards accrual of that arm. Data on these patients will be collected. In order to accrue 6 patients onto Arm C with sufficient tissue for correlatives following surgical resection, a total of 12 patients could be enrolled onto Arm C. In order to accrue 12 patients onto Arm E with sufficient tissue for correlatives following surgical resection, up to 18 patients could be enrolled onto Arm E.

The study duration is expected to be 7 years: 6 years for accrual, and 1 year for follow-up on the last participant enrolled.

Efficacy analyses will be performed separately for each arm. Patients enrolled in arms other than Arm D with a known H3 K27M mutation in their glioma may be included in the analyses of Arm D. Among recurrent glioblastoma patients, large meta-analyses of clinical trials evaluating a wide array of salvage therapeutics (excluding bevacizumab) have consistently reported PFS-6 rates of 9-11% (Ballman 2007; Lamborn 2008; Wu 2010). If the true PFS-6 rate on the current study for patients receiving ONC201 were 30% or higher, there would be interest in further investigation of this treatment regimen. Therefore, this study will be used to detect a difference of 20% using a one-

sided binomial test. Statistically, the hypothesis that will be tested is:

H0: p<=0.1 versus H1: p>0.3
where p is the proportion of patients achieving PFS-6. Enrollment of 30 patients will yield 84% power to detect a 20% difference at an alpha level of 0.05 (one-sided exact test).

The primary efficacy endpoint is PFS-6, defined as the proportion of subjects in the analysis population who remain progression-free for at least six months following initiation of study therapy. Response for the primary analysis will be determined by the investigator assessment, and a confirmation assessment is required per RANO. If patients discontinue protocol therapy at or before 6 months without tumor imaging performed, the patient will be treated in the primary endpoint analysis as a treatment failure. Adjustments will not be made for multiple comparisons.

Secondary efficacy endpoints include: (1) ORR defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using RANO criteria; (2) duration of response, defined as time from first RANO response to disease progression in subjects who achieve a PR or better; (3) progression-free survival (PFS), defined as the time from initiation of study therapy to the first documented disease progression according to RANO or death due to any cause, whichever occurs first; and (4) overall survival (OS).

Additional supportive analyses of duration of response and PFS will be conducted using RANO criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

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, and vital signs.

The predictive utility of intratumoral DRD5 expression will be evaluated in archival tumor specimens based on an inverse correlation with ONC201 efficacy in cancer cell lines. Among the 15 available archival tumor tissue specimens in Arm A, all had expression of DRD2 and 8/17 patients had low expression of DRD5. Patients with PFS>5 month had no detectable expression of DRD5 unlike those with PFS<5 months. In addition, 4/8 DRD2+DRD5- and 0/7 DRD2+DRD5+ patients were still alive with a median follow-up of 47.4 weeks. Based on these findings, DRD2+DRD5- patients are expected to have improved PFS and OS in response to ONC201 administration. For Arm B and Arm C, %DRD2 and %DRD5 positive cells (strong/total) will be quantified using image analysis algorithms for detection of DRD2 and DRD5 immunolabeling area and intensity (Visiopharm VIS software). Arms B and C will be combined for these analyses. Patients with pathologist-verified DRD5 staining area in the biopsy of >0.018% strong positive or >1% total positive will be classified as DRD5+. DRD5+ versus DRD5- patients will be compared for key clinical outcomes using a likelihood

ratio chi-square test (ORR) or log-rank test (PFS, OS). Significance will be declared if the two-sided p-value is <0.05, with no adjustments for multiple comparisons. Because the assay for quantifying the %DRD5 strong positive cells or %DRD5 total positive cells is still being developed to be more precise, the data will also be normalized into Z-scores as a second and independent method of identifying patients as DRD5-positive or negative. Patients with negative Z-scores will be grouped into the DRD5- cohort and patients with positive Z-scores will be grouped into the DRD5+ cohort. The same comparisons for clinical outcome will be performed as above.

Pharmacodynamic effects will be evaluated by assessment of tissue biomarkers based on mechanism of action and preclinical tumor cell sensitivity studies. IHC ATF4, CHOP, and DR5 will be summarized using descriptive statistics.

Intratumoral ONC201 concentration in patients with recurrent GBM will be summarized using descriptive statistics separately for Arm C and E separately. A sample size of 6 achieves 80% power to detect a difference of -1.4 between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 1.4 with an estimated standard deviation of 1.0 and with a significance level (alpha) of 0.05000 using a two-sided one-sample t-test. We are looking for an effect size of 2.9 since the target threshold for intratumoral drug concentrations is 2.9 uM representing the IC50 of ONC201 in cancer cell panels profiled for in-vitro efficacy.

Below you will find a table with calculations of minimal effect size corresponding to differing SDs for a sample size of 6 patients at 80% power and a two sided alpha of 0.5.

Power	N	Alpha	Beta	Mean0	Mean1	S	Effect Size
0.80000	6	0.05000	0.20000	0.0	1.4	1.0	1.435
0.80000	6	0.05000	0.20000	0.0	1.5	1.0	1.435
0.80000	6	0.05000	0.20000	0.0	1.6	1.1	1.435
0.80000	6	0.05000	0.20000	0.0	1.7	1.2	1.435
0.80000	6	0.05000	0.20000	0.0	1.8	1.3	1.435
0.80000	6	0.05000	0.20000	0.0	1.9	1.3	1.435
0.80000	6	0.05000	0.20000	0.0	2.0	1.4	1.435
0.80000	6	0.05000	0.20000	0.0	2.1	1.5	1.435
0.80000	6	0.05000	0.20000	0.0	2.2	1.5	1.435
0.80000	6	0.05000	0.20000	0.0	2.3	1.6	1.435
0.80000	6	0.05000	0.20000	0.0	2.4	1.7	1.435
0.80000	6	0.05000	0.20000	0.0	2.5	1.7	1.435
0.80000	6	0.05000	0.20000	0.0	2.6	1.8	1.435
0.80000	6	0.05000	0.20000	0.0	2.7	1.9	1.435
0.80000	6	0.05000	0.20000	0.0	2.8	2.0	1.435
0.80000	6	0.05000	0.20000	0.0	2.9	2.0	1.435

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Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one. N is the size of the sample drawn from the population. To conserve resources, it should be small. Alpha is the probability of rejecting a true null hypothesis. It should be small. Beta is the probability of accepting a false null hypothesis. It should be small. Mean0 is the value of the population mean under the null hypothesis. It is arbitrary. Mean1 is the value of the population mean under the alternative hypothesis. It is relative to Mean0. Sigma is the standard deviation of the population. It measures the variability in the population. Effect Size, |Mean0-Mean1|/Sigma, is the relative magnitude of the effect under the alternative.

13.2 Interim Analyses

For Arm A, a futility interim analysis will be conducted after 16 patients are enrolled. Since PFS-6 requires at least six months post-study initiation follow-up for subjects without progressive disease, the binary endpoint PFS rate at two months (PFS-2) will be used to determine whether the accrual should be suspended after sixteen patients have accrued. If out of the first 16 patients enrolled, only 7 or less patients are observed to be progression free during the first 2 months after treatment initiation, further accrual in this arm will be discontinued. Assuming exponential distribution, the null and alternative for the PFS6 are translated into 0.44 vs. 0.67 rates for the PFS2. Under these rates the chances of observing 7 or less progression free patients out of the first 16 are 0.6 under the null and 0.046 under the alternative.

For Arm B, D, and F, separately, a futility interim analysis will be conducted after 16 patients who are evaluable for efficacy are enrolled. Since PFS-6 requires at least six months post-study initiation follow-up for subjects without progressive disease, the binary endpoint PFS rate at two months (PFS-2) will be one criteria used to determine whether the accrual should be suspended after sixteen patients have accrued. If out of the first 16 patients who are evaluable for efficacy are enrolled, there is no objective response and only 7 or less patients are observed to be progression free during the first 2 months after treatment initiation, further accrual in this arm will be discontinued. Assuming exponential distribution, the null and alternative for the PFS6 are translated into 0.44 vs. 0.67 rates for the PFS2. Under these rates the chances of observing 7 or less progression free patients out of the first 16 are 0.6 under the null and 0.046 under the alternative.

No interim analyses will be conducted for Arm C or E.

13.3 Statistical Methods for Efficacy Analyses

Efficacy analyses will be performed separately for each arm. Subgroup analyses of the primary tumor location within the brain (e.g. thalamus) and the H3 K27M mutation will be performed across all cohorts. For PFS and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1, as appropriate. Participants without measurable disease will not be included in the analysis of ORR.

13.4 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs for each cohort separately. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by arm either by descriptive statistics or categorical tables.

14. PROTOCOL SIGNATURES

SPONSOR PROTCOL SIGNATURES

Study Title:	Oral ONC201 in Adult Recurrent Glioblastoma
Study Number:	ONC006
Version:	14
Date:	03 June 2021

This clinical trial protocol was reviewed and approved by:

Signature and Date: Allen Melemed Digitally signed by Allen Melemed DN: cn=Allen Melemed, o=Chimerix, ou=Chief Medical Officer, email=amelemed@chimerix.com, c=US Date: 2021.06.14 23:19:51 -04'00'

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APPENDIX A: KARNOFSKY PERFORMANCE STATUS (KPS) CRITERIA

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B: TABLE OF EIAEDS AND NON-EIAEDS*

CYP3A4 enzyme-inducing antiepileptic drugs	Non-CYP3A4 enzyme-inducing antiepileptic drugs
Carbamazepine Oxcarbazepine Phenytoin Fosphenytoin Phenobarbital Primidone	Levetiracetam Valproic acid Lacosamide Gabapentin Topiramate Lamotrigine Tiagabine Zonisamide Clonazepam Clonozam Pregabalin

* This is a partial list. A comprehensive list of EIAEDs can be found at The University of Indiana (http://medicine.iupui.edu/clinpharm/ddis/) has a comprehensive list of EIAEDs which should be consulted.

APPENDIX C: NEUROLOGIC ASSESSMENT IN NEURO-ONCOLOGY (NANO) SCALE

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Study #, Participant # and Initials:_____ _____/_____
Date Assessment Performed (day/month/year): _____
Study time point (i.e. cycle 1, day 1, etc): _____
Assessment performed by (please print name): _____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on

Study #, Participant # and Initials:_____ _____/_____
Date Assessment Performed (day/month/year): _____
Study time point (i.e. cycle 1, day 1, etc): _____

Visual Fields
- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength
- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating

Language
- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness
- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior
- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

APPENDIX D: 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?**	○	○	○	○	○	○	○	○	○	○	○

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Appendix E: STUDY PARTICIPANT SELF-ADMINISTRATION INSTRUCTIONS

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Study Participant Self-Administration Instructions

The study staff will explain how to take the study drug, *ONC201,* but these are points to remember:

Patients will receive ONC201 while in the clinic on day 1 of each cycle. They will take ONC201 at home on days 8 and 15 of each cycle. The study drug, ONC201, will be supplied in capsule form for oral dosing.

Surgical Arm Patients must be evaluated in clinic prior to dosing at home for the first dose after surgery (i.e., the dose taken approximately one week post-surgery).

Patients should take the dose of ONC201 specified by their physician 2 hours prior or 2 hours following food or a meal. **If the patient vomits after taking ONC201, they should not retake the dose. Missed doses will not be made up, if more than 3 days from the intended day of administration.**

ONC201 should be taken with a glass of water and consumed over as short a time as possible. Patients 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.

Please call your doctor or research nurse before taking any new prescription or over-the-counter medications/supplements other than the study drugs.

For any problems, issues, or questions you may have, please contact:_____

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Study Participant Self-Administration Study Drug Diary

Please record how many capsules you take of *ONC201* the time you take them and any comments here below and bring the completed Diary as well as your study drug supply, including empty bottles, to every study visit. This will help us keep track of your study drug and how well you are tolerating it.

Participant Identifier: _____ Cycle Number:_____
Protocol #: *15-318* *ONC201* Assigned Dose: _____ mg
Doctor: _____
Nurse:_____

You will take the following number of _____ each time (per dose) as listed in the table below:

Study Drug Name	# of capsules (tablets) to take per time/dose	# of times/doses each day	Approximate time to take drug
ONC201			__:__ ☐ a.m. ☐ p.m.

Week	Date	Number of ONC201 Capsules	Time of Dose
1			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____
2			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____
3			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____

Participant/Caregiver Signature: _____
Date:_____

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DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	