Expanded access use of ONC201 in a patient with H3K27M glioma

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Treatment Drug: ONC201 (expanded access use)

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Objective

To provide expanded access use of ONC201 treatment for an adult advanced cancer patient with diffuse intrinsic pontine glioma (DIPG) who has exhausted available therapies.

Treatment design

The patient will receive ONC201 at the dose of 625 mg once every week.

Oncoceutics will be consulted prior to any schedule modifications or the addition of other therapy.

Eligibility criteria

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

Inclusion

1. Patient with a DIPG who failed at least one line of prior therapy such as focal radiation therapy
2. Patient must be at least 18 years of age.
3. ECOG performance status ≤ 2.
4. Adequate organ and marrow function as defined below:
    a. Absolute neutrophil count ≥1,000/mm^3 without growth factor use ≤ 7 days prior to treatment (cycle 1 day 1, C1D1)
    b. Hemoglobin ≥8.0 mg/dL without red blood cell transfusion ≤ 3 days prior to C1D1
    c. Total serum bilirubin ≤1.5 X upper limit of normal (ULN)
    d. AST (SGOT)/ALT (SGPT) ≤2 X ULN; ≤ 5 X ULN if there is liver involvement secondary to tumor
    e. Serum creatinine ≤ 1.5 X ULN (OR creatinine clearance ≥ 60 mL/min/1.73 m^2)
5. Ability to understand and the willingness to sign a written informed consent document.
6. Male patient must be surgically sterile or must agree to use effective contraception during the period of the treatment and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.
7. Patient must be able to swallow capsules and retain orally administered medication.

Exclusion

1. Known active bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV)
2. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
3. Active or prior plasma cell leukemia (defined as either 20% of peripheral WBC comprised of plasma/CD138+ cells or an absolute count of 2 x 10^9/L).
4. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
5. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.
6. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with treatment participation or ONC201 administration, or may interfere with the interpretation of treatment results, or in the judgment of the investigator would make the patient inappropriate for entry into ONC201 treatment.

INTRODUCTION

This is an expanded access use protocol for an adult patient with DIPG who underwent focal radiation therapy and was subsequently enrolled in PNOC009 – using convection enhanced delivery of nanolilposomal CPT-11 (see Appendix C for complete medical history).

1.1 Indication

ONC201 is being investigated in clinical trials in adult patients with advanced cancer.

1.2 Background on Treatment Agent

ONC201 (TIC10) is a selective DRD2 antagonist that activates the integrated stress response (ISR) in inactivates prosurvival Akt and ERK signaling in tumor cells along with induction and activation of the TRAIL apoptosis pathway [2]. 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. In summary, preclinical studies suggest that ONC201 is an orally active antitumor agent with a remarkably benign safety profile given its broad-spectrum activity demonstrated in a variety of aggressive cancer models.

1.2.1 Preclinical Efficacy

ONC201 induces broad-spectrum cell death in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that render resistance to chemotherapies and targeted agents. ONC201 induces caspase-mediated apoptosis in cancer cell lines and exhibits broad-spectrum cytotoxicity *in vitro*. ONC201 has demonstrated single agent anti-tumor effects in several solid tumor models that include subcutaneous (Figure 1.1), orthotopic, and transgenic models in a wide range of malignancies in preclinical models (e.g. glioblastoma multiforme, triple-negative breast cancer, colorectal cancer and non-small cell lung cancer). Beyond solid tumors, ONC201 has also demonstrated striking efficacy in liquid tumors that include leukemia, multiple myeloma, and B-cell lymphoma (Figure 1.2).

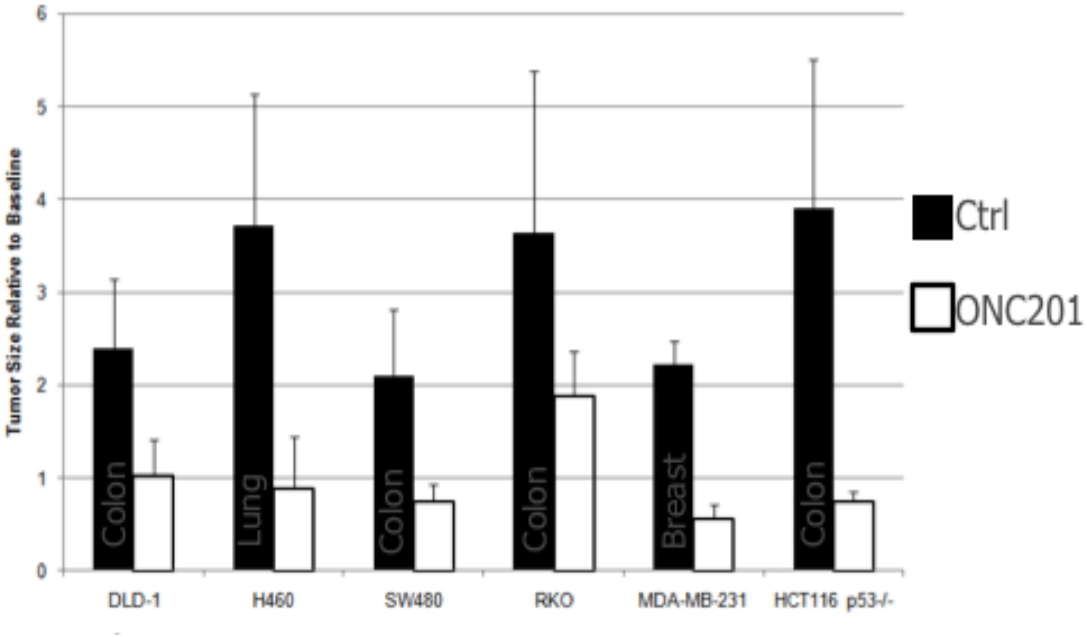

Figure 1.1 ONC201 antitumor activity in subcutaneous xenografts. Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and is relative to the tumor size on the day of administration.

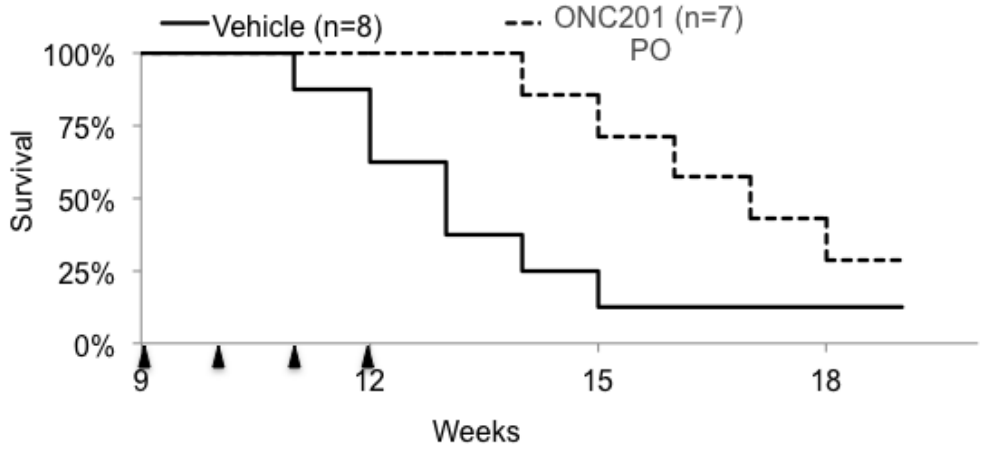

Figure 1.2 ONC201 prolongs the survival of transgenic mice with lymphoma. Overall survival of Eμ-myc treated once a week during weeks 9-12 with ONC201 (PO, qwk). P=.00789 determined by log-rank test.

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 in the preclinical model. 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. The 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.

1.2.2 Mechanism of Action

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

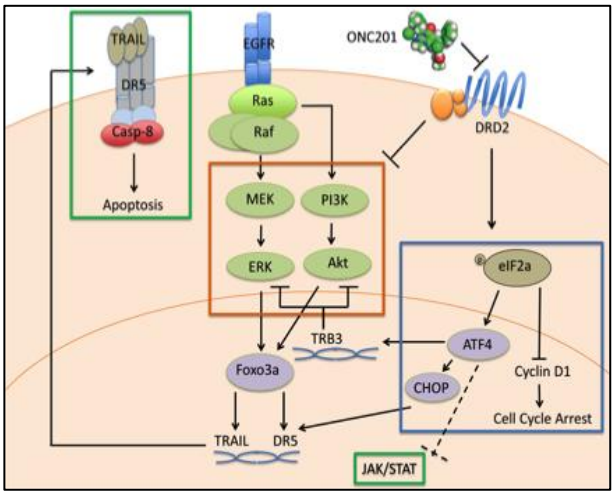

Figure 1.3 Proposed model of ONC201 in tumor cells.

Downstream of target engagement, ONC201 activates the integrated stress response (ISR), which is the same signaling pathway activated by ER stress-inducing compounds such as proteasome inhibitors (e.g. bortezomib). When the ISR is activated by ER stress-inducing compounds, the pathway is often referred to as the ER stress response. ONC201 causes an early-stage increase in the phosphorylation of eIF2-alpha at serine 51, which results in attenuation of protein translation and upregulation of the transcription factor ATF4 (Figure 1.3). 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.

ONC201 has been reported to decrease the phosphorylated active forms of the oncogenic kinases Akt, MEK, and ERK. The decreased phosphorylation of Akt and ERK causes decreased kinase activity, leading to dephosphorylation of its substrates that include the mutual substrate Foxo3a [9]. ONC201-induced effects on these signaling pathways have been demonstrated in several tumor types in vitro with diverse genetic mutations in p53, KRAS, PTEN, and others**.** Targeting the Ras signaling pathway, which includes two arms ending at the effector kinases Akt and ERK, has been an unattainable therapeutic goal for decades [6]. Ras and its upstream activating receptors such as EGFR are very commonly activated in human cancer through mutations, amplification, or other mechanisms. This critical signaling pathway transduces stimulus signals from the extracellular environment into the nucleus to regulate genes that drive survival and proliferation. While the field widely accepts the enormous impact that inhibiting Ras would have in oncology, directly targeting Ras in tumors has not been performed successfully in the clinic. The challenge underlying this absence lies in the fact that Ras is a GTPase rather than a routinely drugged class of proteins such as a kinase. Nevertheless, targeting effector kinases downstream of Ras have been vigorously pursued in recent years as a chemically viable strategy by combining small molecule PI3K/Akt inhibitors with MEK/ERK inhibitors. While the dual inhibition of these pathways is widely reported to be synergistic it is plagued by toxicity and other limitations [4, 5, 7]. This combinatorial approach has several efficacy-limiting shortcomings that include toxicity [8] as these kinases are important for several physiological processes, compounding toxicity, drug-drug interactions, and the need for synchronous delivery to tumors.

In contrast to Akt and MEK inhibitors, ONC201 inactivates Akt and ERK indirectly in tumor cells while these kinases are uninhibited in normal cells. The lack of dual inhibition in normal cells means that ONC201 does not induce death of normal cell , allowing ONC201 to be safe at efficacious doses in cancer models in vitro and in vivo [1]. The inhibition of Akt and ERK in cancer cells is sustained following drug removal, maintained in the face of upstream mutations (e.g. KRAS), and is independent of upstream ligand stimulation (e.g. EGF). Furthermore, the ability of ONC201 to inhibit these two kinases as a single molecule results in concomitant dual inactivation that yields synergistic efficacy and also eliminates complications with combination therapy such as compounding toxicity and drug-drug interactions.

Recent gene expression profiling studies in solid and liquid tumor cell lines revealed transcriptome changes consistent with induction of the ER stress response. Subsequent experiments validated that ONC201 activated the pro-apoptotic arm of ER stress in cancer cells, which is also activated by proteasome inhibitors. CHOP is a pro-apoptotic transcription that is induced as a critical effector of the maladaptive apoptotic ER stress response. Robust induction of CHOP expression in response to ONC201 treatment has been observed in multiple models in a response- and time-dependent manner. ER stress may be linked to prior observations related to Akt and ERK signaling in solid tumor cells with ONC201 treatment, as previously reported with ER stress-

inducing compounds. Based on these findings, CHOP, pERK, pAkt, TRAIL, and DR5 should be evaluated for clinical utility as biomarkers in patients receiving ONC201 treatment.

1.2.3 Nonclinical Safety/Toxicology Studies in Animals

In rats and dogs ONC201 was better tolerated when administered orally compared to intravenously. In rat non-GLP studies, the No-Observed Adverse Effect Level (NOAEL) was 225 mg/kg with oral administration compared to 100 mg/kg with a 2 hour infusion and 50 mg/kg with a 30 minutes infusion. Non-GLP clinical observations in rodents included decreased activity, altered gait, and mortality. In dog non-GLP studies, the NOAEL in doses 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 GLP dog studies, the NOAEL was at least 42 mg/kg. Observations were limited to decreased activity, decreased food consumption, emesis, salivation, and/or soft, loose or mucous feces. In rat GLP studies, the NOAEL was at least 125 mg/kg. Observations included decreased activity, decreased food consumption, decreased body weight, and abnormal stance and gait. Minor changes in serum chemistries were noted, largely in the 225 mg/kg rat cohort, which included slight increases in cholesterol and chloride. The significance of these findings is unknown as other clinical chemistry and histology did not corroborate this observation (e.g. liver findings). Rats receiving 125 or 225 mg/kg ONC201 had mild edema and inflammation that was primarily submucosal in the stomach and was completely resolved by day 19.

1.2.3.1 Non-GLP Safety Studies

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

Non-GLP toxicology studies in rats

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

The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 30-minute intravenous infusion was 50 mg/kg. The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 2-hour intravenous infusion was 100 mg/kg. Administration of 100 mg/kg

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

Non-GLP toxicology studies in dogs

In parallel to non-GLP toxicology studies in rats, the ability of beagle dogs to tolerate ONC201 was explored. No deaths were observed at any doses in dogs. The NOAEL following the 30-minute intravenous infusion of ONC201 to beagle dogs is considered to be at least 33.3 mg/kg. The 2 hour-intravenous infusion of 16.7 mg/kg ONC201 was not associated with any clinical signs of toxicity. Therefore the NOAEL following a 2 hour-intravenous infusion of ONC201 to beagle dogs is considered to be greater than 16.7 mg/kg, though higher doses were not explored as the oral route was selected for further development based on observations in rats. The NOAEL with oral ONC201 was considered to be at least 120 mg/kg in dogs. Clinical observations at doses of 66.7 to 120 mg/kg were limited to emesis and changes in fecal consistency.

1.2.3.2 GLP Toxicology and Safety Studies

Single Dose Oral Toxicity Study in Dogs (GLP)

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

Although not statistically significant, there were some dose-related decreases in group mean food consumption for the first week following dosing. The 120 mg/kg females had statistically significantly decreased group mean food consumption compared to the vehicle control group on Days 14, 15 and 18. There were no clinical signs of toxicity noted following a single dose of 4.2 mg/kg ONC201. At a dose of 42 mg/kg and 120 mg/kg, some dogs had clinical observations at approximately 1 hour post-dose including decreased activity, emesis, salivation, and/or soft, loose or mucous feces. Of uncertain relationship to ONC201 administration was the unusual finding of

mononuclear cell inflammation in the blood vessels of the brain, which was multifocal and mild in one high dose female at Day 3, multifocal and minimal in one high dose female at Day 19, and minimal and focal in one control female at Day 19. Similar findings were not noted in any male animal.

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

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

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

There was no mortality observed in this study. There were no definitive ONC201-related effects on coagulation parameters, clinical chemistry parameters, gross findings at necropsy. There were no clinical signs of toxicity noted at single doses up to 125 mg/kg ONC201. There were no ONC201-related statistically significant changes in hematology parameters or clinical chemistries outside of the historical control range for these values.

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

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

Changes in brain and liver weights were noted but did not occur in a dose-dependent manner and no microscopic changes were noted 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.

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

A GLP study was performed to determine the potential effects of ONC201 dihydrochloride on respiratory function in rats following a single oral gavage administration. Twenty four (6/group) male rats received 0, 12.5, 125, or 225 mg/kg ONC201 by oral gavage and were monitored in plethysmographic chambers. The oral administration of ONC201 dihydrochloride at 12.5 and 125 mg/kg did not induce any biologically relevant effects on respiratory rate, tidal volume or minute volume in conscious male rats. A marginal to moderate transient decrease in respiratory rate and minute volume was observed following the oral administration of ONC201 dihydrochloride at 225 mg/kg, which resolved by 2 hours.

1.2.4 Pharmacokinetic Studies

1.2.4.1 Pharmacokinetic Studies in Animals

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

In dogs, exposure to ONC201 following oral gavage dosing at 4.2, 42, and 120 mg/kg ONC201 was dose-dependent and increased with greater ONC201 dose levels (Figure 1.6). Exposure to ONC201 was similar in male and female dogs with the observation that all mean male C_{max} and AUC values were slightly greater than those corresponding female values. Elimination of ONC201 from plasma was similar between the mid and high dose levels; mean $t_{1/2}$ ranged from 4.6 to 7.8 hours. Mean $t_{1/2}$ following the low dose of 4.2 mg/kg was ~1 hour [the half-life determined for dogs in the low dose group may represent more of a distribution phase half-life rather than the terminal plasma elimination half-life]. Overall elimination of ONC201 was greater following the low dose.

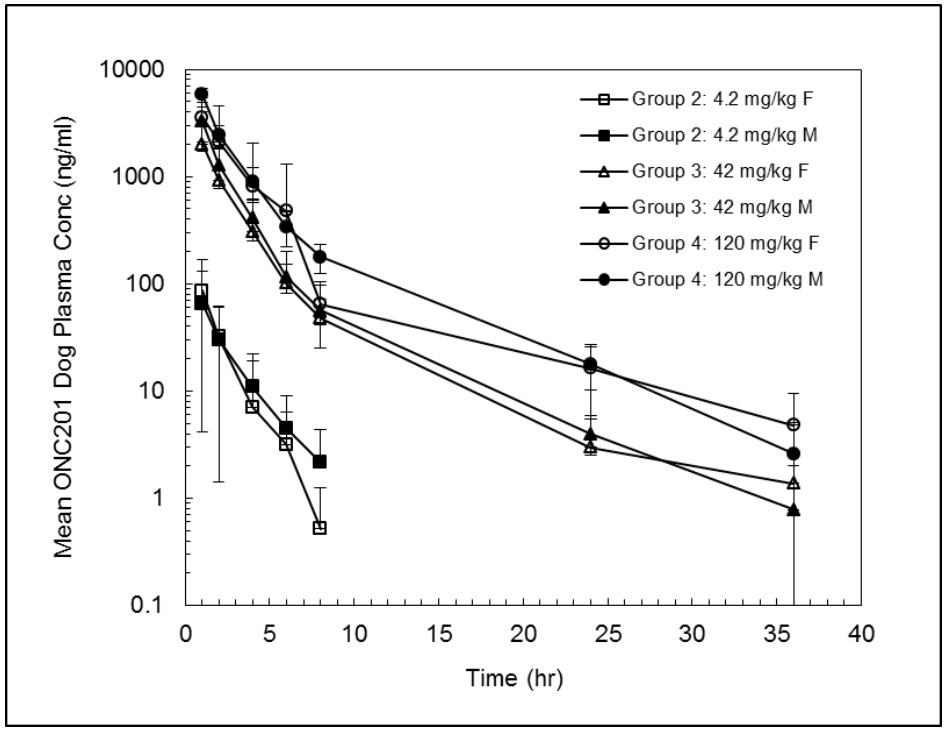

Figure 1.6 Dog Plasma Concentrations (Mean ± SD) of ONC201 Plotted as a Function of Time Following a Single Oral Gavage Dose to Male and Female Beagle Dogs.

1.2.4.2 Pharmacokinetic Studies in Humans

In 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 1.7; 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. A increase in volume of distribution was observed with increasing patient weight or BSA, as expected. Trends of decreasing exposure with increasing weight were observed in plots of Cmax/Dose and AUC/Dose versus patient weight. Weight normalized CL/F was plotted versus Dose, showing a similar trend to un-normalized CL/F.

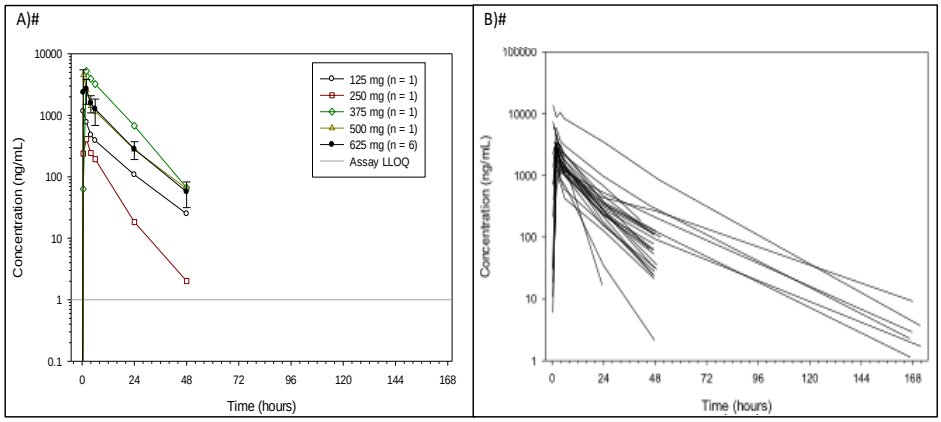

Figure 1.7: Mean ONC201 plasma concentrations versus time following the first dose of ONC201. Concentrations are shown as (A) A mean for each dose cohort, or (B) for individuals treated at 625 mg.

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

1.3 Clinical Studies

Below are summaries of ONC201 clinical trials, as of December 2016. The current recombined phase 2 dose (RP2D) of ONC201 in adults is 625mg every one week.

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 monoagent 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 six cycles and remains on therapy. 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 [3] 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 twelve 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 these patients. 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, 11 patients have been enrolled in this study using 2 administration schedules – once every 3 weeks and once every week. 6 patients were dosed at once every 3 weeks schedule at various dose escalation cohorts (125mg, 250mg, 365mg, 500mg, 625mg) and 5 patients were dosed on weekly cohorts (125mg, 250mg, 375mg, 500mg). No SAEs or AEs of any grade have been reported to Oncoceutics as possibly, probably, or definitely related to study drug. There were reported instances of febrile neutropenia, lung infection (pneumonia), gastrointestinal disorders and abdominal pain. None of these adverse event 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, 3 patients have been enrolled at 125 mg and 1 patient at 250 mg dosed once every 3 weeks. In addition, 3 patients have been enrolled at the weekly schedule (125mg or 625mg). No drug-related 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, 6 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.

Study #15-318 (NCT02525692) is a Phase II study of ONC201 in patients with recurrent glioblastoma, being conducted at Massachusetts General Hospital and Dana Farber Cancer Institute. 17 patients have been treated at 625mg ONC201 once every three weeks. In this study, a patient with a H3.3 K27M mutant GBM had a PR with a 82% decrease in tumor volume after 8 doses of drug and is still on therapy, while another patient remains disease-free. Seven of these 17 patients experienced 18 AEs that were attributed by the investigator as possibly-related to study drug and 1 probably-related to study drug. One patient had a Grade 1 nausea, diarrhea, constipation and fatigue. The same patient experienced non-serious and unexpected Grade 1 and Grade 2 allergic reactions that were possibly related to ONC201 and another Grade 1 allergic reaction that was attributed as probably related to ONC201 (positive on rechallenge and symptoms were mitigated by de-sensitization). Another patient had a Grade 1 fatigue and a Grade 2 anorexia event. Three other patients had a Grade 1 fatigue, 1 patient had a Grade 1 hypophosphatemia and one patient had Grade 1 thrombocytopenia. These AEs were attributed to be possibly-related to ONC201.

1.4 Rationale

ONC201 is a first-in-class small molecule with antitumor activity in difficult-to-treat cancers as demonstrated using *in vitro*, *ex vivo*, and *in vivo* models. 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 sample that are refractory to chemotherapy and targeted therapies, including bortezomib refractory multiple myeloma. ONC201 is effective in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that render resistance to chemotherapy and targeted therapies.

ONC201 will be administered once every week. This dosing schedule was selected based on the sustained intratumoral activity of the molecule for at least several days to weeks following a single dose of the drug (Figure 1.7). Furthermore, varying dose frequencies (range of twice a week to every two weeks) of ONC201 in a preclinical cancer model showed that the more frequent dosing did not yield any increased efficacy.

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 C_{max}) with maximal efficacy by 5-fold and thus higher doses may not be explored.

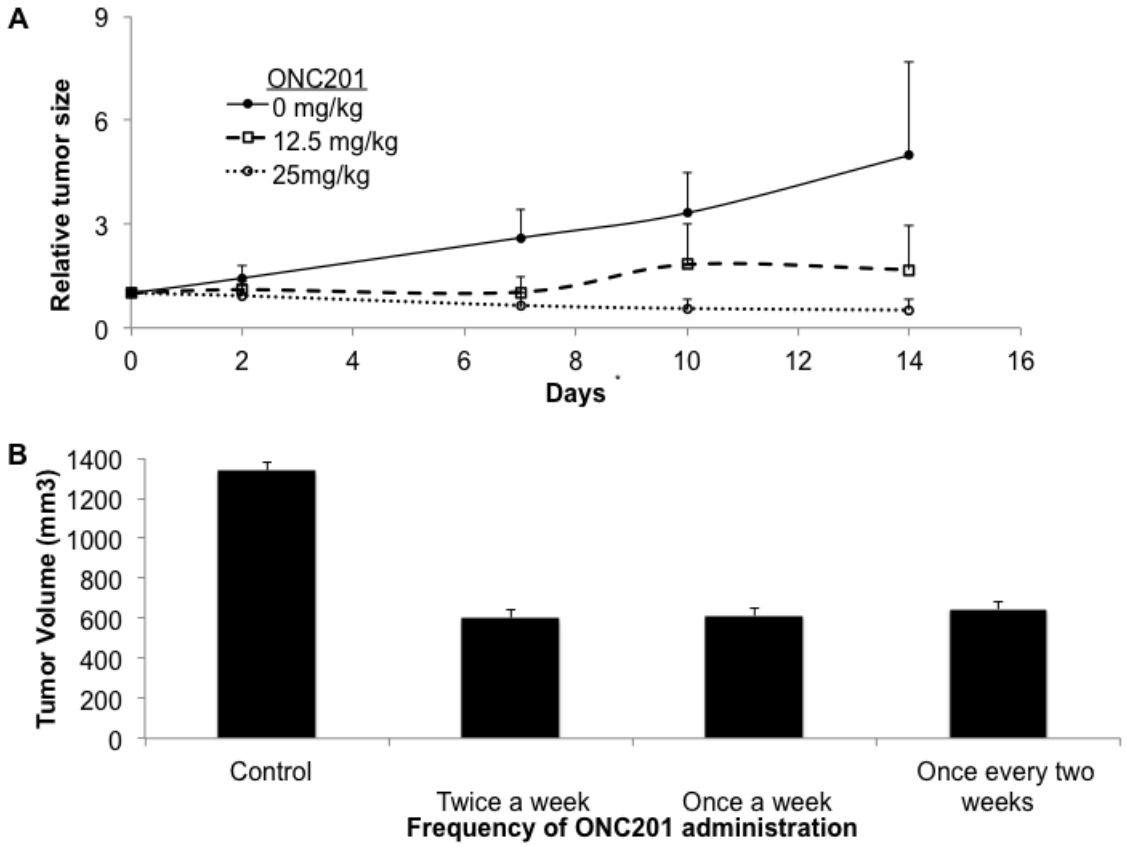

Figure 1.7 ONC201 has sustained and saturable efficacy in subcutaneous xenografts. (A) HCT116 xenograft tumor relative to baseline size following treatment with ONC201 at indicated dose (p.o.). (B) Tumor volume of HCT116 subcutaneous xenografts in athymic nude mice receiving intravenous doses of ONC201 at 25mg/kg per dose (n=8). Treatment was initiated on day 0. The total dose for twice a week was 6 mg, once a week was 3 mg, and once every two weeks was 2 mg.

2 OBJECTIVES

2.1 Objectives

To provide ONC201 treatment as expanded access use for an adult patient with advanced cancer who has exhausted all available therapies.

3 TREATMENT DESIGN

3.1 Overview

The patient will receive ONC201 at the starting dose of 625 mg once every week. As per the Principal Investigator's discretion, additional medication(s) approved for the patient's solid tumor may be included when the disease has progressed on ONC201. Oncoceutics will be consulted prior to any additional medication.

3.2 Dose and Planned Scheme

Treatment with ONC201 will be administered once every week at 625 mg. One cycle is defined as 21 days (three weeks), with day 1 defined as the day of treatment administration. ONC201 will be provided as an oral capsule. The patient may discontinue therapy at any time for any reason.

Oncoceutics will be consulted prior to any schedule modifications or the addition of other therapy. Combination therapy may also be considered based on Principal Investigator discretion and in consultation with Oncoceutics.

3.3 Contraception

If the patient has a partner of childbearing potential, he must take precautions to prevent pregnancy of the partner since the effects of this drug on sperm are unknown. These restrictions should remain in force for 90 days from the last dose of investigational agent. Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. The definition of effective contraception should be in agreement with local regulation and based on the judgment of the principal investigator or a designated associate. A suggested definition of adequate contraception is the use of double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device).

4 TREATMENT

4.1 Drug Supply

4.1.1 Formulation, Packaging and Storage

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

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

The ONC201 bottle label bears the following information:

ONC201 Capsules, 125mg

For Oral Use Only

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

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

Sponsor: Oncoceutics, Inc

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

Figure 3.1: Investigational drug label

4.1.2 Drug Accountability

Upon receipt at the investigative site, treatment drug product must be stored at room temperature in the original packaging. The drug should be protected from light and excessive humidity in a monitored, locked, secure area with limited access. Storage area temperature conditions must be monitored and recorded daily. All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. Site staff must instruct the patient on how to store and administer oral treatment drug agents that are dispensed for at-home administration.

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

4.1.3 Drug Administration

The capsules are not to be chewed or broken but need to be swallowed whole. The patient should take designated capsules of ONC201 at approximately the same time each day and should not consume food or a meal 2 hours before or after swallowing the capsule(s).

4.2 ONC201 Administration

Patient will receive 625 mg of ONC201 per week. The treatment drug, ONC201, will be supplied in capsule form for oral dosing.

Patient should take designated capsules of ONC201 at approximately the same time on each day of drug administration. Patient will be instructed to not eat for 2 hours before or after dosing. If the patient vomits after taking ONC201, they should not retake the dose. Missed doses will not be made up.

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

4.3 Duration of Therapy

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

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

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

5 DOSING DELAYS/DOSE MODIFICATIONS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications

Below are dose modifications for adverse events that are attributable to treatment drug, including: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia – only if associated with clinically significant bleeding. If a patient experiences other adverse events, or several adverse events and there are conflicting recommendations based on Grade, the investigator will use the recommended dose adjustment that reduces the dose. Dose modifications will be made based on an adverse event that occurs during any time during a cycle.

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

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

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

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

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

5.1 Concomitant Medications

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

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

6 PROCEDURES

All procedures below are completed according to Appendix A: Schedule of Procedures.

- Patient signature on informed consent form – must be completed prior to dosing
- Medical history, including tumor history, history of other disease processes (active or resolved), concomitant illnesses, and demographics.
- Baseline signs and symptoms
- Vital signs
- Height
- Weight
- Physical exam
- ECOG performance status
- Hematology, blood chemistry, coagulation, urinalysis
- Concomitant medications
- Circulating pharmacodynamic analyses (see Section 6.1)
- Patient reported outcomes (see Section 7.3)

Biological materials outlined below will be collected and sent to Oncoceutics. Please contact Oncoceutics (#215-966-6115; rohinton.tarapore@oncoceutics.com) prior to preparing the shipment.

6.1 Circulating Pharmacodynamic Analyses

Prolactin and other proteins will be measured in serum as pharmacodynamic markers. One red-top tube (without anti-coagulant) of at least 10 mL of blood will be collected at the following time points: Baseline and 2 hours after the first dose of ONC201; C1D8 (pre-dose); C1D15 (pre-dose); pre-dose for the first day of cycle 2. Blood will also be drawn at the time of tumor assessment by radiographic imaging. The tubes should be labeled as: ONC016-name of site-patient's initials-date and time of the blood draw (hours and minutes).

6.2 Plasma Analyses

For the patient, one (1) EDTA tube of 10 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. All samples will be processed to produce plasma that will be stored cryogenically until analysis. A detailed procedure is provided in Appendix D.

6.3 Collection of Tumor Specimens during SOC Biopsies

Collection of tumor specimens during standard of care biopsies after initiating ONC201 administration is optional. If leftover tissue is available from a standard of care biopsy, fresh tumor tissue will be collected and divided into 2 samples:

- One sample will be flash frozen for RNA, DNA, protein, and drug concentration analyses.
- The other sample will be formalin-fixed and paraffin-embedded tissue blocks will be used to prepare 15 unstained FFPE slides for immunohistochemistry. An additional 10 FFPE tissue slides will be requested for the archival tumor tissue samples.

6.4 Patient Withdrawal

The patient may withdraw at any point during the protocol.

7 ASSESSMENTS

7.1 Safety Evaluations

Safety assessments include collection of AEs, SAEs, and safety laboratory.

7.2 Disease Evaluations

Disease assessments, including radiographic imaging, will be part of standard of care as per the treating physician's discretion (typically every 8 weeks). These results should be sent to Oncoceutics (rohinton.tarapore@oncoceutics.com) as they become available.

7.3 Patient Reported Outcomes

At the beginning of each treatment cycle (i.e., every 21 days) the patient will complete the MDASI questionnaire (Appendix B). Scanned PRO forms should be sent to Oncoceutics (pharmacovigilance@oncoceutics.com) as they become available.

7.4 Duration of Follow-up

The patient will be followed post-treatment every 30 days (±7 days) until death, withdrawal of permission to record at least survival data, or patient is lost to follow-up. When available, tumor imaging will be followed for 6 months after stopping treatment. The patient will be contacted every 30 days to assess for -treatment-related toxicities, initiation of any new anti-cancer treatments, and survival status. Contact may be performed by a site visit, telephone contact, e-mail, or mail. The date of death, initiation of any new anti-cancer treatments and date of last contact should be documented if this information is available.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Oncoceutics. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequalae resolve or stabilize at a level acceptable to the investigator, and Oncoceutics concurs with that assessment.

All “unexpected”(defined below) and/or “serious” (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the regulatory file.

The principal investigator has the obligation to report all serious adverse events to the IRB and Oncoceutics.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped treatment must be reported. This includes the period in which the protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after treatment discontinuation need only be reported if a relationship to ONC201 treatment drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

8.2 Reporting Period

Serious adverse events require immediate notification to Oncoceutics beginning from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the treatment protocol, i.e., prior to undergoing any treatment-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of treatment through last patient visit.

If the patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Exposure in utero;
- Exposure during breast feeding.

Worsening of signs and symptoms of the malignancy during the treatment should be reported as adverse events in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.4 Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the malignancy under treatment (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome during the treatment protocol or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTC grade 5 (see Section 8.7, Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5 Hospitalization

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization is considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission for a procedure required by
- the treatment protocol;
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.6 Severity Assessment

If required on the adverse event case report forms, the investigator will use the following definitions of Severity in accordance with Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (Version 4.03) to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

Table 8.1: General AE Grading Assessment

Grade	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in CTCAE but may be used in certain circumstances)
1	**MILD** adverse event
2	**MODERATE** adverse events
3	**SEVERE** adverse events
4	**LIFE-THREATENING OR DISABLING** adverse events
5	**DEATH RELATED TO** adverse events

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.7 Causality Assessment

The investigator’s assessment of causality must be provided for all adverse events (serious and non-serious). An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator’s final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on treatment records.

In addition, if the investigator determines a serious adverse event is associated with treatment procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.8 Exposure *in utero*

An exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
2. A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If a woman becomes pregnant or suspects that she is pregnant while participating in this treatment, she must inform the investigator immediately and permanently discontinue treatment drug. Oncoceutics must be immediately (with 24 hours of awareness) be contacted. The pregnancy must be followed for the final pregnancy outcome.

If any patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must submit this information to Oncoceutics. In addition, the investigator must submit information regarding environmental exposure to this drug in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage). This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify Oncoceutics of the outcome. The reason(s) for an induced abortion should be specified. A serious adverse event case is created with the event of ectopic pregnancy.

8.9 Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate. .

8.9.1 Serious Adverse Event Reporting Requirements

Investigators must also report to Oncoceutics any SAE that occurs after the initial dose of treatment, during treatment, or within 3 days of the last dose of treatment on the local institutional SAE form or the FDA Form 3500A (MedWatch) form. Oncoceutics must be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Oncoceutics must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero and exposure during breast feeding cases.

The serious adverse event report must include, but need not be limited to: (1) the date of the event; (2) designation of the report as an initial report or a follow-up report, (3) identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports; (4) clinical site; (5) the Principal Investigator; (6) NIH Protocol number; (7) FDA's Investigational New Drug (IND) Application number; (8) vector type , e.g., adenovirus; (9) vector subtype, e.g., type 5, relevant deletions; (10) gene delivery method, e.g., in vivo, ex vivo transduction; (11) route of administration, e.g., intratumoral, intravenous; (12) dosing schedule; (13) a complete description of the event; (14) relevant clinical observations; (15) relevant clinical history; (16) relevant tests that were or are planned to be conducted; (17) date of any treatment of the event; and (18) the suspected cause of the event. These items may be reported by using the recommended Adverse Event Reporting Template available on NIH OBA's web site at: http://www4.od.nih.gov/oba/rac/documents1.htm, or you can use an MedWatch form.

Within 24 hours of learning of any SAE occurrence, SAE reports and any other relevant safety information are to be forwarded to:

- **pharmacovigilance@oncoceutics.com, and**
- **the Oncoceutics facsimile number: 1-844-245-7650**

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

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

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

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient treatment patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event. For all serious adverse events, the investigator is obligated to pursue and provide information to Oncoceutics in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Oncoceutics to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Oncoceutics or its designated representative.

8.9.2 Potential Cases of Drug-Induced Liver Injury

While ONC201 is not expected to cause significant elevations in liver enzymes, such occurrence is of special interest to regulatory agencies. Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. If the patient presents with the following laboratory abnormalities, he should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

A. If the patient has AST or ALT baseline values within the normal range, and subsequently presents with:
    a. AST or ALT ≥3 times the upper limit of normal, and
    b. Total bilirubin ≥2 times the upper limit of normal with no evidence of hemolysis, and
    c. Alkaline phosphatase ≥2 times the upper limit of normal or not available.

B. If the patient has pre-existing AST or ALT baseline values above the normal range and subsequently presents with:
    a. AST or ALT ≥2 times the baseline values and ≥3 times the upper limit of normal, or
    b. AST or ALT ≥8 times the upper limit of normal (whichever is smaller) concurrent with:
        i. Total bilirubin of ≥2 times the upper limit of normal and increased by one upper limit of normal over baseline, or
        ii. Total bilirubin of >3 times the upper limit of normal (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≥2 times the upper limit of normal or not available.

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria A or B, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

9 DATA HANDLING, IMAGE SUBMISSION AND RECORD KEEPING

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

9.1 Data Reporting

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

9.2 Submission of Images

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

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

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

1) **FTP Transfer:** Coordinate with Rohinton Tarapore (rohinton.tarapore@oncoceutics.com) to set up FTP transmission of images.

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

   Rohinton Tarapore
   Oncoceutics Inc.
   3624 Market Street
   Suite #5E
   Philadelphia, PA 19104
   #215-966-6115

9.3 Data Collection

9.3.1 Data Collection Forms

Qualified clinical trials study monitors that represent Oncoceutics will complete remote and on-site monitoring.

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

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

1. The Sponsor or designee will conduct an initiation meeting remotely prior to the start of the treatment. The treatment protocol, procedures and CRFs will be reviewed in detail and the treatment personnel will be trained, if needed, to carry out the procedures defined in the protocol.
2. The Investigator will store the treatment-related regulatory and site documentation (e.g. treatment logs and forms) in a Site Binder.
3. All written treatment 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 treatment 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 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 database will be validated using appropriate validation processes
6. The Sponsor or designee may perform a regulatory audit of the site, and may include a complete review of the overall treatment conduct, regulatory documentation, and selected patient CRFs and source documents.

9.3.2 Registration and Eligibility

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

9.3.3 Patient Consent Form

Informed consent must be obtained before protocol-specified procedures or interventions are carried out. The investigator will explain the nature of the treatment and will inform the patient that participation is voluntary and that they can withdraw at any time. A copy of the signed consent form will be given to the patient and the original will be maintained with the patient'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 patient. 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 patient 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 patient should receive a copy of the signed and dated written informed consent form and any other written information provided to the patient, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to the patient.

9.3.4 Site Monitoring

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this treatment 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 treatment.

Contractors of the Sponsor will conduct routine monitoring or audit activities for this treatment. The general scope of such visits would be to inspect treatment 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.

10 ETHICS

10.1 Institutional Review Board (IRB)

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 treatment 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 protocol 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 treatment-related documentation, including source document and CRFs, long enough to allow the sponsor to use the data to support marketing applications. If this treatment 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 treatment documents. For such studies conducted under IND exemption, records will be retained for a minimum of seven (7) years past official treatment protocol termination.

10.2 Ethical Conduct of Expanded Access Treatment Use

The expanded access treatment use will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

10.3 Patient Information and Consent

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

The informed consent form must be by the IRB and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

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

11 DISCONTINUATION CRITERIA

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

12 REFERENCES

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Appendix A: Schedule of Procedures

Cycle	**SC**	**Cycle 1 (21 days)**			**Cycle 2+ (21 days)**			**Long Term Follow-Up**
Cycle Day		1	8	15	1	8	15	Every 30 days
Visit Window [a]	None	None	± 3 Days		± 7 Days			± 7 Days
Assessment								
Informed Consent	X							
Medical History and Demographics	X							
Physical examination [b]	X	X	X	X	X			
Vital signs	X	X	X	X	X			
Performance score	X	X	X	X	X			
CBC	X [f]	X	X	X	X			
Serum chemistry, liver function tests [c]	X	X	X	X	X			
Urinalysis	X	X	X	X	X			
MDASI questionnaire		X			X			
Adverse events		X	X	X	X			X [h]
Concomitant medications	X	X	X	X	X			
Disease assessment (MRI)		X			X [g]			X [i]
Circulating Pharmacodynamic Analyses [d]		X	X	X	X [g]			
Plasma Analyses [e]		X						
ONC201 administration		X	X	X	X	X	X	
Survival status and other therapies								X [h]

Footnotes:

a. Visit window only applies to observation, not ONC201 administration.
b. Height should be recorded during Screening only.
c. Liver function tests: AST and ALT, serum creatine, total serum bilirubin. Additional tests may be performed at the discretion of the treating physician.
d. One red-top tube (without anti-coagulant) of at least 10 mL of blood will be collected at the following time points: C1D1 (Baseline and 2 hours post-dose ONC201); C1D8 (pre-dose); C1D15 (pre-dose); C1D2 (pre-dose).
e. One EDTA tube of 10 mL of blood will be collected on C1D1 pre-dose ONC201, and again 2 hours (± 15 minutes) post-dose.
f. Screening CBC to be performed ≤ 3 days prior to C1D1.
g. Disease assessment (MRI) to occur every 8 weeks (± 14 days) per standard of care after C1D1. One EDTA tube of 10 mL of blood will be collected for circulating pharmacodynamic analyses at the time of disease assessments.
h. Follow-up contact every 30 days after coming off treatment to assess for study-treatment related toxicities, initiation of any new anti-cancer treatments, and survival status. Contact may be performed by a site visit, telephone contact, e-mail, or mail.
i. End of Treatment disease assessment (MRI) to occur 30 days (± 7 days) after last ONC201 administration. When available, tumor imaging will be followed for 6 months after patient stops treatment.

Appendix B: 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?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

MDASI-BT - 2006

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

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

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

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

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

MDASI-BT - 2006

Appendix C: Patient History.

P.R. is a 40 year old male who presented with a history of mild dysphagia, dysarthria, and numbness of his right face in summer 2017. On 8/14/17, an MRI of the brain at an external medical facility revealed a heterogeneously T2 hyperintense, non-enhancing expansile lesion centered in the pons, most consistent with a brainstem glioma. He was treated with focal radiation therapy of 59 Gy from 9/7/2017 - 10/20/2017. He was enrolled on PNOC 009 on 11/20/2017. He had his first CED performed on Nov 21, 2017 (nl CPT11 60 mg infused). His 2nd CED procedure was on January 10, 2018 (nl CPT11 60 mg infused). Immediate side effects from this procedure included right sided weakness (which improved by time of discharge), facial weakness (which improved by time of discharge), and ongoing diplopia (since first CED procedure). His most recent MRI report showed stable disease. P.R. elected to come off PNOC009 study on 2/16/2018 due to side effects (most bothersome was the ongoing diplopia). His performance score is 80.

Appendix D: Blood Sample Collection and Processing

At the specified time points, blood will be collected in the pre-specified tube type(s), processed, aliquoted, frozen and shipped to the designated analytical laboratory. Refer to the treatment protocol for blood sample collection time points.

Plasma sample supplies

For Plasma Blood Collection

Becton-Dickinson Plastic Whole Blood tube with spray-coated K2EDTA
Lavender top, Vacutainer
Catalogue 367525
Tube Size: 16x100
Draw Volume: 10mL

For Plasma Aliquots

Wheaton 2mL Ext FS CryoElite
Blue Cap Patch Sterile
Catalogue W985868

Serum sample supplies

For Serum Blood Collection

Serum Tube, Increased Silica Act Clot Activator, Silicone-Coated Interior
Red Top Vacutainer
BD Catalogue 366430
Tube Size: 16 X 100
Draw Volume: 10mL

For Serum Aliquot Storage

Wheaton 2mL Ext FS CryoElite
Yellow Cap Patch Sterile
Wheaton Catalogue W985866

Collection of Blood

Check the expiration dates on the vacutainer tubes before collecting blood. If the tubes have expired, discard them. Do not substitute another brand of collection tube. Prepare the blood collection tubes by affixing labels to each tube before collecting specimens from the patient.

Using standard aseptic venipuncture techniques, draw the blood sample into the specified collection tube. For time points requiring both plasma and serum blood draws, the plasma sample should be drawn first. Remove tourniquet as soon as blood flow into the first vacutainer tube is established; excessive use of tourniquets can lead to hemoconcentration and falsely elevated results. Ensure each vacutainer is full to provide accurate blood:additive ratios. Mix blood tubes by gently inverting each tube 5 times. On the label, clearly print with a black permanent marking pen: ONC016-name of site-patient's initials-date and time of the blood draw (hours and minutes).

Place the full blood collection tube(s) into a resealable clear biohazard bag. Arrange prompt pick up by, or delivery to, the local laboratory since blood must be processed and frozen within 2 hours of collection.

Plasma Processing

After blood collection, centrifuge the 1 lavender top vacutainer tube (10 mL) at 1500 g (3000 rpm) for 15 minutes until the plasma and the cells are well separated. On the 2 blue cap vials clearly print the Oncoceutics identifier "ONC016-name of site-patient's initials-date and time of the blood draw (hours and minutes. Transfer ~0.5 mL of plasma into each of the 2 labeled blue cap vials and freeze them at -80°C immediately. Processing of plasma should be initiated and completed within 2 hours of blood collection.

Serum Processing

After blood collection, let the red top vacutainer tubes stand at room temperature until a clot has formed (approximately 30 minutes). As soon as the clot has formed, centrifuge the red top vacutainer tube at 1500 g (3000 rpm) for 15 minutes until the serum and the cells are well separated. On the 2 yellow cap vials clearly print "ONC016-name of site-patient's initials-date and time of the blood draw (hours and minutes). After the centrifugation has ended, immediately transfer ~1.5 mL of serum into each of the 2 yellow top vials and freeze them at -80°C immediately. If 10 mL of blood could not be collected, transfer equal amounts of serum into each of the 2 yellow top vials and freeze them at -80°C immediately. Processing of serum should be initiated and completed within 2 hours of blood collection.

Shipping

Contact Oncoceutics (rohinton.tarapore@oncoceutics.com) for instructions before preparing the shipment.