Protocol Title: Oral ONC201 in Relapsed/Refractory Multiple Myeloma

Protocol Number: ONC007 (NCT02863991)

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CAUTION: Investigational New Drug

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

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Protocol Synopsis

Proposed Indication:
Oral ONC201 is intended for treatment of adult patients with relapsed/refractory multiple myeloma for whom no standard therapy is available.

Rationale:
ONC201 is an orally bioavailable first-in-class small molecule with demonstrated antitumor activity in preclinical models of difficult-to-treat solid and liquid tumors without imparting significant toxicity. Multiple myeloma has been selected for evaluation in this trial based on preclinical efficacy as well as the mechanism of action of ONC201 that involves engagement of the integrated stress response that leads to downstream inactivation of Ras signaling and induction of the TRAIL pathway.

Objectives and endpoints

Primary Objective
- Determine the antitumor efficacy of ONC201 in combination with dexamethasone.

Secondary Objectives
- Evaluate the overall safety profile of ONC201 in combination with dexamethasone.
- Assess the pharmacodynamic (PD) effects of ONC201 in combination with dexamethasone.
- Assess effect of ONC201 in combination with dexamethasone on survival endpoints.

Primary Endpoint
- Overall response rate (ORR) using the International Myeloma Working Group response criteria.

Secondary Endpoints
- Overall safety profile of ONC201 as characterized by type, frequency, severity, timing and relationship to study therapy of adverse events and laboratory abnormalities.
- Effects of ONC201 on pharmacodynamic (PD) markers.
- Effects of ONC201 on survival endpoints (i.e., progression-free survival, time to progression, and duration of response).

Study design
This is a Phase 1/2 open-label study of ONC201 administered orally once every week in combination with dexamethasone to patients with relapsed/refractory multiple myeloma.

In Phase 1 of the study, patients will receive 625 mg ONC201 once every week in combination with dexamethasone using a 3+3 dose escalation design that will evaluate up to 625mg ONC201 weekly with 20mg dexamethasone. Three weeks is defined as a treatment cycle.

Phase 1 of the study will involve a safety cohort of at least 6 relapsed/refractory multiple myeloma patients who will receive ONC201 and dexamethasone.

In Phase 2 of the study, patients will receive 625mg ONC201 once every week. Dexamethasone will be administered at a dose determined in Phase 1. Patients may not cross over from Phase 1. Tumor assessments will be conducted using the International Myeloma Working Group response criteria. The study plans to enroll 42 patients over a period of 2 years.

Eligibility criteria

Inclusion

1. Patients must be refractory to, or not a candidate for, established therapy known to provide clinical benefit for their malignancy.
2. Measurable disease M protein component in serum (at least 0.5 g/dL) and/or urine (if present) (>=0.2 g excreted in a 24 hour collection sample), or serum free light chain level ≥10 mg/dL, provided the serum free light chain ratio was abnormal.
3. Able to swallow and retain oral medication.
4. All previous therapies for cancer, including radiotherapy, major surgery and investigational therapies discontinued for ≥ 14 days (≥ 28 days for mitomycin C or nitrosoureas) before study entry, and all acute effects of any prior therapy resolved to baseline severity or Grade ≤ 1 Common Terminology Criteria for Adverse Events (CTCAE v4.03), except alopecia or parameters defined in this eligibility list.
5. Age ≥ 18 years.
6. ECOG performance status ≤ 1.
7. 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. Platelets ≥50,000/mm^3 without platelet transfusion ≤ 3 days prior to C1D1
    c. Hemoglobin ≥8.0 mg/dL without red blood cell transfusion ≤ 3 days prior to C1D1
    d. Total serum bilirubin ≤1.5 X upper limit of normal (ULN); subjects with >1.5X upper limit of normal require approval of medical monitor.
    e. AST (SGOT)/ALT (SGPT) ≤2 X ULN; ≤ 5 X ULN if there is liver involvement secondary to tumor
    f. Serum creatinine ≤ 1.5 X ULN (OR creatinine clearance ≥ 30 mL/min/1.73 m^2)
    g. Serum or urine pregnancy test (for females of childbearing potential) negative ≤7 days of starting treatment
8. Ability to understand and the willingness to sign a written informed consent document and comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.
9. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception during the period of the trial 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.

Exclusion

1. Active inflammatory gastrointestinal disease, chronic diarrhea (unless related to underlying malignancy or prior related treatment) or history of abdominal fistula, gastrointestinal perforation, peptic ulcer disease, or intra-abdominal abscess within 6 months prior to study enrollment. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.
2. Pregnancy or breast feeding.
3. Current active treatment in another clinical study.
4. Active bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV)
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness that is not well controlled.
6. 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).
7. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
8. Subjects with serum calcium (corrected for albumin) ≥ 12 mg/dL
9. 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.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.
11. Actively receiving medications that have the risk of Torsades de Pointes or are string cytochrome P450 inhibitors or inducers.

Statistical methods

Overall response rate (ORR) will be determined with the corresponding 95% exact confidence interval. Descriptive statistics will be provided for selected demographic, safety, PD and biomarker data by dose, dose schedule and time, response rate, and time to progression as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities

Examination[1]	Baseline	Cycle 1				Cycle 2	Cycle 3+	Follow up[2]
Day	-28	1	2& 3	8	15	1	1	1
Informed Consent	X							
Medical History	X							
Inclusion/Exclusion Criteria	X	X						
Concurrent meds	X	X				X	X	X
Physical exam[3]	X	X				X	X	X
Performance Status (ECOG)	X	X						
Vital signs[4]	X	X				X	X	X
Pregnancy Test	X							
Urinalysis	X	X				X	X	
Toxicity Assessment[5]	X	X		X	X	X	X	X
12-Lead EKG[6]	X	X			X	X		
Bone Marrow Aspiration/Biopsy[7]	X			X			X[7]	X[7]
Serum Protein Electrophoresis	X	X				X	X	X

[1] All assessments have a ± 2 business day window, except where specified.
[2] 4 weeks (28 days) after off study visit.
[3] Height (baseline only) and weight included.
[4] Blood pressure, HR, temperature and respiratory rate.
[5] Toxicity assessments will be performed at each patient encounter. Baseline signs and symptoms prior to C1D1 must also be assessed.
[6] EKG assessment performed in triplicate. Cycle 1 day 1 and cycle 2 day 1 will be obtained at 2 hours (+15 minutes) post-dose. Cycle 1 day 15 and cycle 2 day 15 will be taken pre-dose
[7] Bone marrow biopsy will be performed within 45 days of cycle 1 day 1. Bone marrow biopsy to be repeated at relapse. If possible, repeat bone marrow biopsy 6 hours after the second dose is administered (C1D8). If bone marrow biopsy cannot be carried out at any time point, an aspirate will be needed. Restaging should be performed within 7 days prior to the scheduled visit date. Bone marrow biopsy will also be performed for suspected complete response as per IMWG criteria.

Examination[1]	Baseline	Cycle 1				Cycle 2	Cycle 3+	Follow up[2]
Serum Quantitative Immunoglobulins[8]	X	X				X[8]	X[8]	X[8]
Serum β_2-Microglobulin[8]	X	X				X[8]	X[8]	X[8]
Serum free light chains (kappa and lambda) with ratio[8]	X	X				X[8]	X[8]	X[8]
Serum and Urine Immunoelectrophoresis[8]	X	X				X[8]	X[8]	X[8]
24-Hour Urine M-protein electrophoresis[9]	X	X				X[9]	X[9]	X[9]
Urine collection[10]		X	X					
Skeletal X-rays[11]	X						X	X
Hematology[12]	X	X		X	X	X	X	X
Serum Chemistry[13]	X	X		X	X	X	X	X
Coagulation Profile[14]	X					X	X	X
Blood draws for PK/PD[15]		X	X	X	X	X	X	X

[8] As needed to evaluate response. In patients with IgD myeloma, IgD levels must be followed if available.

[9] Repeat 24-hour urine M-protein determination monthly in patients who initially had measurable urinary M-protein and for whom this is being used in response criteria. Patients who initially lack urine M-protein, or in whom the M-protein disappears, must have the 24-hour urine M-protein obtained every 12 weeks. Immunoelectrophoresis or immunofixation of serum and urine do not need to be repeated unless the M-spike disappears on electrophoresis.

[10] Urine collection: A 24 hour urine will be collected when the patient visits the clinic 24 hours after first dose of ONC201 on Cycle 1 Day 2. Spot urine collection will be carried out on Cycle 1 Day 2 and Day 3..

[11] Including lateral skull, axial skeleton, and long bones.

[12] WBC plus differential, Hgb, PLT.

[13] Glucose, BUN, Creatinine, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase , LDH, Na+, K+, Ca++, Phosphate, Uric acid, Magnesium. Eligibility parameters must be met at baseline, but not necessary to meet criteria after treatment initiation.

[14] PT/PTT, INR.

[15] Blood draws for PK/PD evaluations: will be collected at baseline and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8, Cycle 1 Day 15; pre-dose for the first day of cycle 2, cycle 3 and every odd cycle beyond cycle 3. Blood will also be collected at the follow-up visit at the end of treatment.

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1 INTRODUCTION

This study will evaluate the efficacy of ONC201 administered in combination with dexamethasone to patients with relapsed/refractory multiple myeloma. The study plans to enroll 42 patients who will receive ONC201 once every week and will have tumor assessment using International Myeloma Working Group response criteria.

1.1 Proposed Indication

ONC201 is intended for treatment of adult patients with relapsed/refractory multiple myeloma for whom no standard therapy is available.

1.2 Background on Study Agent

ONC201 (TIC10) is an orally bioavailable first-in-class small molecule that directly antagonizes DRD2 to activate 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 et al., 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. In summary, preclinical studies suggest that ONC201 is an orally active antitumor agent with a favorable 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).

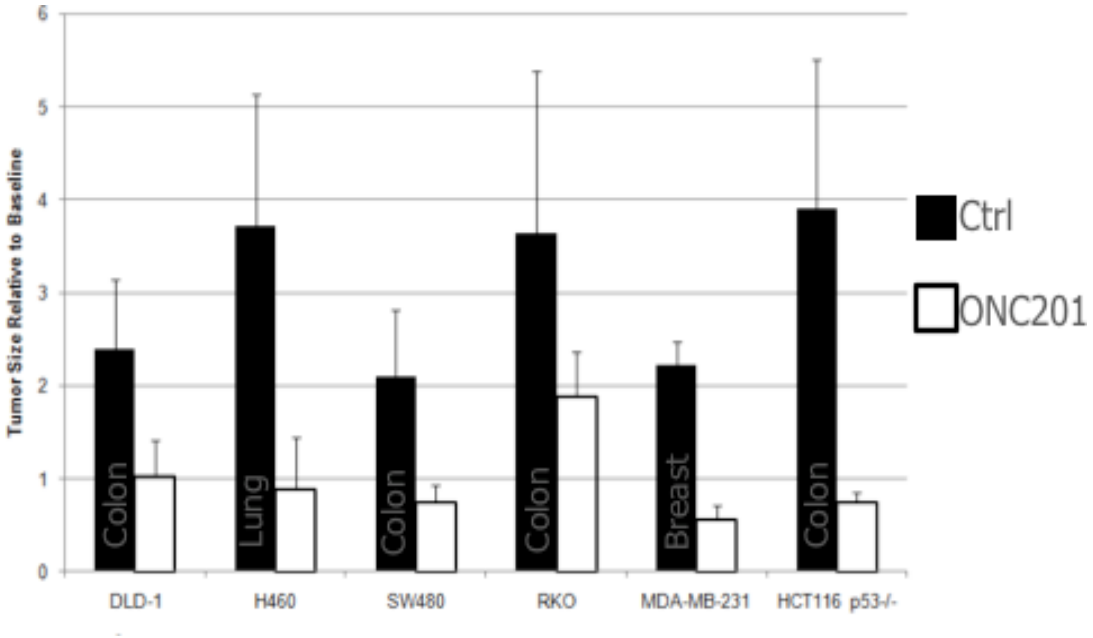

Figure 1.1 ONC201 antitumor activity in subcutaneous xenografts. Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and is relative to the tumor size on the day of administration.

Beyond solid tumors, ONC201 has also demonstrated striking efficacy in liquid tumors that include leukemia, multiple myeloma, and B-cell lymphoma (Figure 1.2). Multiple myeloma is highly sensitive to agents such as proteasome inhibitors that induce the ER stress response, the same pathway triggered by ONC201 treatment by a unique mechanism. Furthermore, multiple myeloma cell lines are particularly sensitive to ONC201 compared to other tumor types (Figure 1.3-1.4). In accordance with its unique mechanism, ONC201 is effective despite evolved resistance to the proteasome inhibitor bortezomib in multiple myeloma cell lines. Thus, the mechanism of action and preclinical efficacy results for ONC201 indicate that multiple myeloma is a highly sensitive tumor type that warrants clinical investigation of its monoagent antitumor activity.

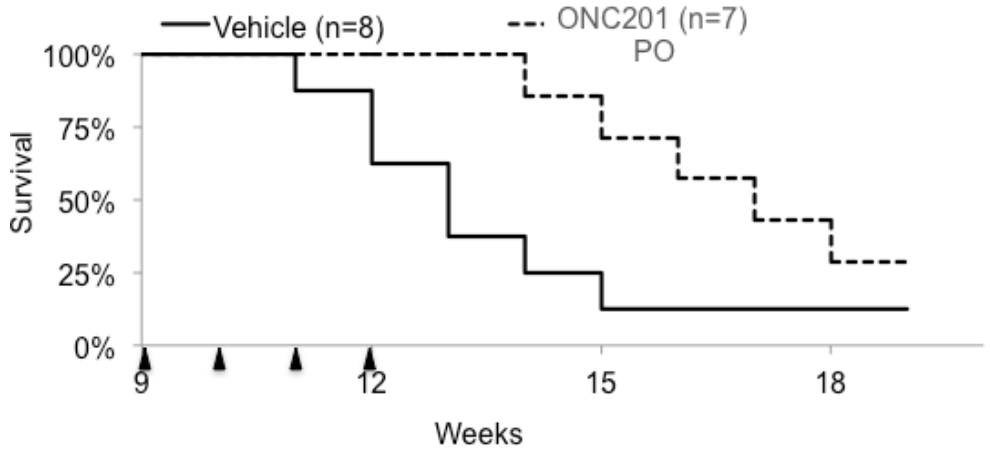

Figure 1.2 ONC201 prolongs the survival of transgenic mice with lymphoma. Overall survival of Eμ-myc treated once a week during weeks 9-12 with ONC201 (PO, qwk). P=.00789 determined by log-rank test.

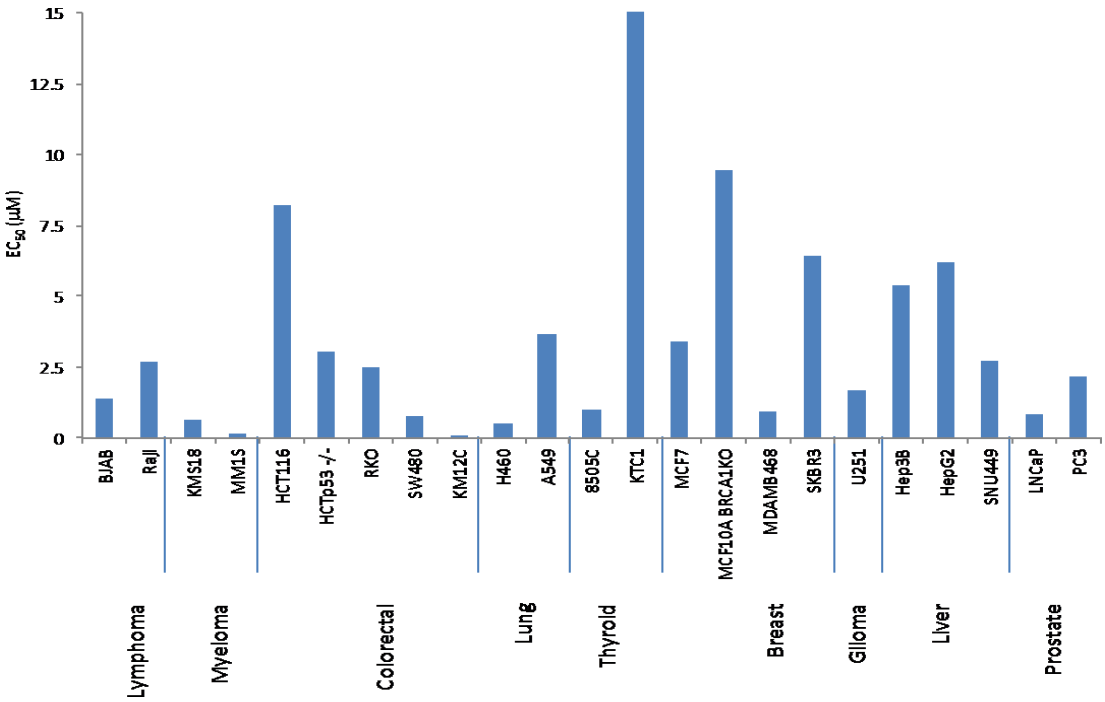

Figure 1.3 ONC201 broad-spectrum activity in cancer cell lines with high sensitivity in multiple myeloma. Cancer cell lines EC50 extrapolated from by the ATP-dependent Cell Titer Glo assay (72 hrs, n=2).

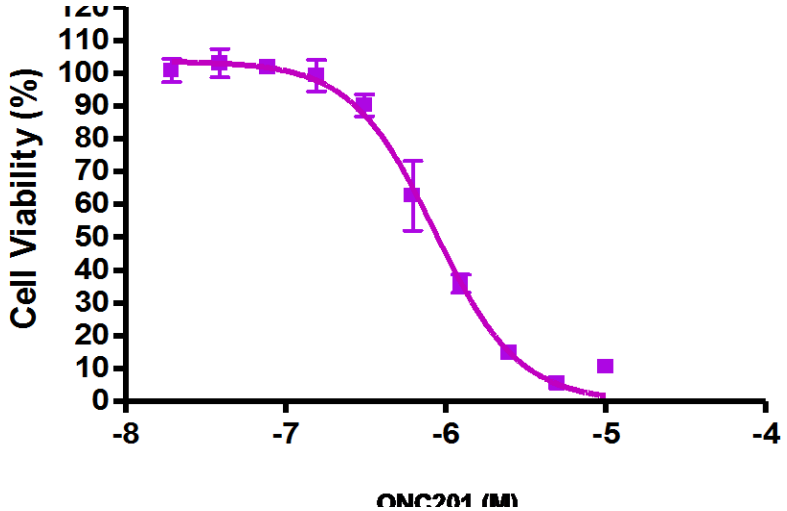

Figure 1.4 ONC201 causes a dose-dependent eradication of multiple myeloma cell culture. RPMI8226 cells were incubated with indicated concentrations of ONC201 (72 hrs, n=3).

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 was identified through a phenotypic screen as a small molecule that induces p53-independent upregulation 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.

ONC201 appears to activate 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 1.5). ATF4 up regulates 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.

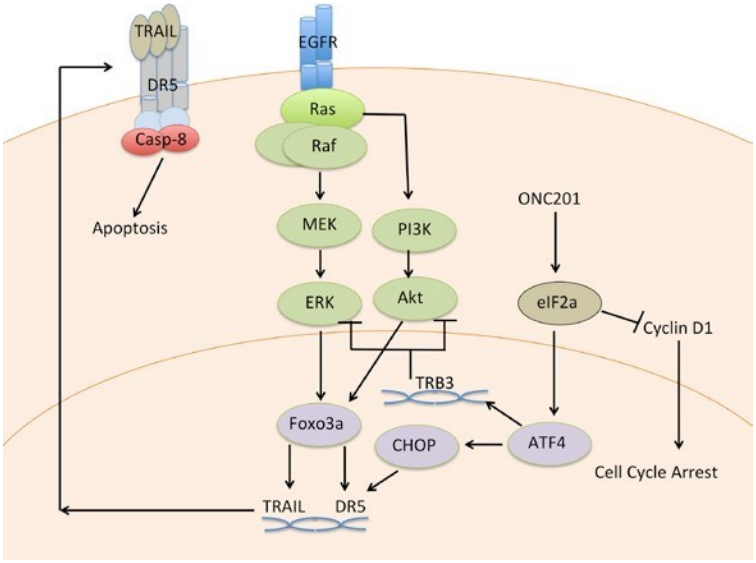

Figure 1.5 Proposed model of ONC201 MOA in tumor cells

In summary, ONC201 appears to activate the ISR that attenuates protein translation and activates ATF4, which causes induction of genes that lead to apoptosis. ATF4 and CHOP also downregulate Akt and ERK activity that cooperatively induce complementary downstream apoptotic effects. Preliminary evidence suggests that 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.

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.

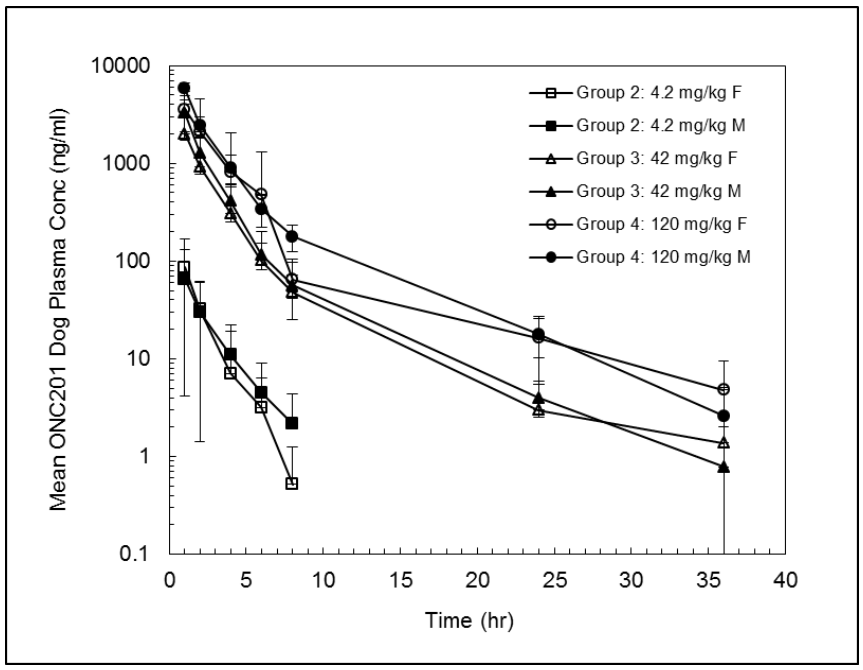

Figure 1.6 Dog Plasma Concentrations (Mean ± SD) of ONC201 Plotted as a Function of Time Following a Single Oral Gavage Dose to Male and Female Beagle Dogs.

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 1.1). 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.

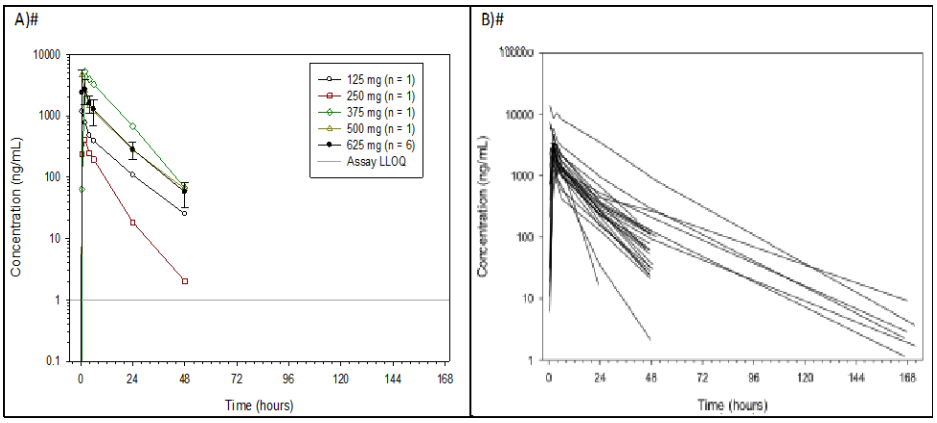

Figure 1.7: Mean ONC201 plasma concentrations versus time following the first dose of ONC201. Concentrations are shown as (A) A mean for each dose cohort, or (B) for individuals treated at 625 mg.

Table 1.1 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

1.3 Clinical Studies

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 2 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 2 dose. Ten evaluable patients (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 2.9 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. Dyspnea and fatigue was observed in a few patients, which was attributed to their underlying disease. No drug-related toxicities Grade >1 were observed in any patients in this study.

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 8 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 et al; 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. As of September 8, 2016, there have been no reports of 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.

Additional clinical studies of ONC201 are enrolling, including a Phase I clinical trial in advanced solid tumors and multiple myeloma, a Phase I/II clinical trial in relapsed/refractory acute leukemias and high-risk myelodysplastic syndrome (MDS), a Phase I/II clinical trial in relapsed/refractory Non-Hodgkin's lymphoma (NHL) and a Phase II clinical trial in bevacizumab-naïve glioblastoma multiforme (GBM).

1.4 Rationale

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. 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. Multiple myeloma is highly sensitive to ER stress-inducing agents that trigger the ISR such as proteasome inhibitors used to treat multiple myeloma. 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. Multiple myeloma have been selected for evaluation in this trial based on preclinical efficacy as well as the mechanism of action of ONC201 that involves engagement of the ISR, inactivation of Ras signaling, and induction of the TRAIL pathway that should be effective in these tumors based on preclinical and clinical evidence. Administration of ONC201 with dexamethasone in this study is based on preclinical evidence that ONC201 synergizes with dexamethasone in multiple myeloma cell lines (Figure 1.8).

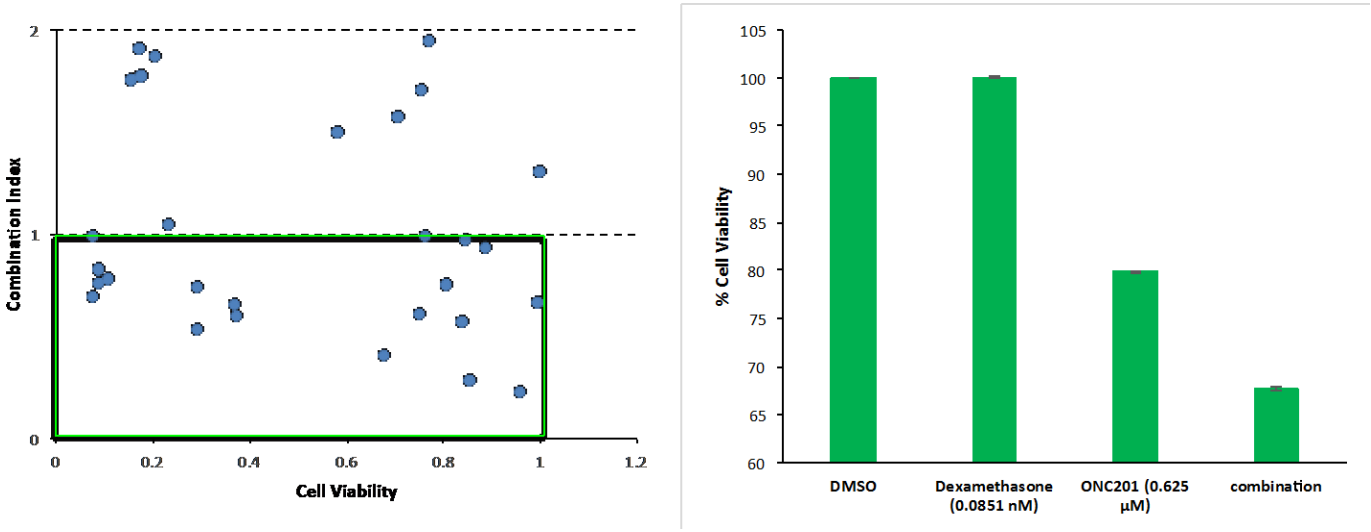

Figure 1.8 ONC201 synergizes with dexamethasone in multiple myeloma. Combination indices (left) and exemplary combination results (right) for cell viability of RPMI-8226 cells treated with ONC201 and/or dexamethasone (72 hrs, n=2).

ONC201 will be administered once every week. This infrequent dosing schedule was 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 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Determine the antitumor efficacy of ONC201 in combination with dexamethasone.

2.1.2 Secondary Objectives

- Evaluate the overall safety profile of ONC201 in combination with dexamethasone.
- Assess the pharmacodynamic (PD) effects of ONC201 in combination with dexamethasone.
- Assess effect of ONC201 in combination with dexamethasone on survival endpoints.

2.2 Endpoints

2.2.1 Primary Endpoint

- Overall response rate (ORR) using the International Myeloma Working Group response criteria.

2.2.2 Secondary Endpoints

- Overall safety profile of ONC201 as characterized by type, frequency, severity, timing and relationship to study therapy of adverse events and laboratory abnormalities.
- Effects of ONC201 on pharmacodynamic (PD) markers.
- Effects of ONC201 on survival endpoints (i.e., progression-free survival, time to progression, and duration of response)

3 STUDY DESIGN

3.1 Overview

This is a Phase 1/2, open-label study of ONC201 in combination with dexamtheasone in adult patients with relapsed/refractory multiple myeloma. This trial intends to explore the antitumor efficacy of orally administered ONC201 at 625 mg weekly in patients receiving concomitant dexamethasone, using the International Myeloma Working Group response criteria.

Throughout the study, AEs, SAEs, laboratory values, vital signs, physical examination findings, ECOG performance status, and EKGs will be obtained. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Study drug may be discontinued if a patient experiences study treatment-related toxicity.

Serial blood samples to measure relevant biomarkers will be collected at prespecified time points as indicated in Section 7.

3.2 Number of Patients

Phase 1 is expected to enroll up to 12 patients and Phase 2 will enroll up to 30 evaluable patients over the course of 2 years. The actual sample size will depend on the clinical results.

3.3 Dose and Planned Scheme

In Phase I, ONC201 is inteneded to be administered once every week at 375mg or 625mg. Dexamethasone will be administered same day of each ONC201 administration. One cycle is defined as 21 days (three weeks), which is also the dose-limiting toxicity (DLT) window.

Phase 1 of the study involves a 3 + 3 dose escalation with a starting dose of 375mg ONC201 followed by an escalation to 625mg ONC201. This will allow assessment of the safety, tolerability, pharmacodynamic effects, and efficacy of two doses of weekly ONC201 in combination with dexamethasone. Dexamethasone will be administered at 20mg weekly. In the unexpected event that >1/6 patients in the first cohort experience a DLT, dose de-escalation will proceed by a 3 + 3 design using 8mg dexamethasone and 375mg ONC201. Further dose de-escalation would involve step-wise decreasing 125mg increments of ONC201. Dose de-escalation below 125mg ONC201 and 8 mg dexamethasone will not be permitted.

Once a recommended phase 2 dose (RP2D) has been determined in Phase I based on a favorable benefit/risk ratio (anticipated to be 625mg ONC201 with 20mg dexamethasone), the study will progress to Phase 2 of the study.

4 ELIGIBILITY CRITERIA

The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1 Inclusion

1. Patients must be refractory to, or not a candidate for, established therapy known to provide clinical benefit for their malignancy.
2. Measurable disease M protein component in serum (at least 0.5 g/dL) and/or urine (if present) (>=0.2 g excreted in a 24 hour collection sample), or serum free light chain level ≥10 mg/dL, provided the serum free light chain ratio was abnormal.
3. Able to swallow and retain oral medication.
4. All previous therapies for cancer, including radiotherapy, major surgery and investigational therapies must be discontinued for ≥ 14 days (≥ 28 days for mitomycin C or nitrosoureas) before study entry, and all acute effects of any prior therapy must have resolved to baseline severity or Grade ≤ 1 Common Terminology Criteria for Adverse Events (CTCAE v4.03), except alopecia or parameters defined in this eligibility list.
5. Age ≥ 18 years
6. ECOG performance status ≤ 1
7. Adequate organ and marrow function as defined below:
    h. Absolute neutrophil count ≥1,000/mm^3 without growth factor use ≤ 7 days prior to treatment (cycle 1 day 1, C1D1)
    i. Platelets ≥50,000/mm^3 without platelet transfusion ≤ 3 days prior to C1D1
    j. Hemoglobin $\geq$8.0 mg/dL without red blood cell transfusion ≤ 3 days prior to C1D1
    k. Total serum bilirubin $\leq$1.5 X upper limit of normal (ULN) ; subjects with >1.5X upper limit of normal require approval of medical monitor.
    l. AST (SGOT)/ALT (SGPT) ≤2 X ULN; ≤ 5 X ULN if liver dysfunction is felt to be secondary to tumor burden
    m. Serum creatinine ≤ 1.5 X ULN (OR creatinine clearance ≥ 30 mL/min/1.73 m^2)
    n. Serum or urine pregnancy test (for females of childbearing potential) negative ≤7 days of starting treatment
8. Ability to understand and the willingness to sign a written informed consent document and comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.
9. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. Male patients must be surgically sterile or must agree to use effective contraception during the period of the trial 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.

4.2 Exclusion

1. Active inflammatory gastrointestinal disease such as chronic diarrhea (unless related to underlying malignancy or prior related treatment) or history of abdominal fistula, gastrointestinal perforation, peptic ulcer disease, or intra-abdominal abscess within 6 months prior to study enrollment. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.
2. Pregnancy or breast feeding
3. Current active treatment in another clinical study
4. Active bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV)
5. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness that is not well controlled.
6. 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)
7. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
8. Subjects with serum calcium (corrected for albumin) ≥ 12 mg/dL
9. 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.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.
11. Actively receiving medications that have risk of Torsades de Pointes or are strong cytochrome P450 inhibitors or inducers.

4.3 Contraception

During the study, fertile female patients must take precautions to prevent pregnancy since the effects of the study medication on the fetus are unknown. Male patients with partners of childbearing potential 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).

5 STUDY TREATMENTS

5.1 Drug Supply

5.1.1 Formulation, Packaging and Storage

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

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

The study drug bottle label bears the following information:

ONC201 Capsules, 125mg

For Oral Use Only

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

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

Sponsor: Oncoceutics, Inc.

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

Figure 3.1: Investigational drug label

5.1.2 Drug Accountability

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

Accountability for study drug product is the responsibility of the investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient-by-patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. A written explanation must be provided for any discrepancies. Patients are to be instructed on proper accountability of the take-home study

drugs and will be instructed to return any unused drug in the original packaging along with their completed diary cards at the appropriate clinic visits. The investigator must destroy or return all unused drug product provided.

5.2 ONC201 Administration

Patients will receive 625 mg of ONC201 on an outpatient basis. The study drug, ONC201, will be supplied in capsule form for oral dosing. Patients should take designated capsules of ONC201 at approximately the same time on each day of drug administration. Patients will be instructed to not eat for 2 hours pre and 2 hours post 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. 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. 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.

Dexamethasone will be obtained and administered per standard of care guidelines for multiple myeloma patients. Administration of dexamethasone is recommended approximately 6 hours (+ 2 hours) after ONC201.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of ONC201 with other concomitantly administered drugs through the cytochrome P450 system, the case report form will capture the concurrent use of all other drugs, over-the-counter medications, and/or alternative therapies. Concomitant medications that have risk of Torsades de Pointes, or are strong cytochrome P450 inhibitors or inducers, are not allowed.

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source documents and case report form (CRF) that will be provided by the Sponsor.

5.4 Duration of Therapy

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

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

- The Sponsor chooses to discontinue the study: for example if severe or life threatening toxicities are encountered by other enrolled patients in the clinical trial or the dose to pharmacokinetics or pharmacodynamics relationship plateaus.

Patients will be followed for three years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment ≥ 14 days or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance with protocol requirements (determined via meeting with PI, applicable Sub-I, clinical research coordinator, and patient)
- Unacceptable adverse event(s). Note, a DLT in and of itself may not be an unacceptable adverse event. However, any grade 4 study-drug related AE is unacceptable and will lead to withdraw. The investigator will use his/her opinion, in consultation with the PI, to determine if a study-drug related AE is unacceptable, acceptable, or clinically insignificant (also acceptable).
- Withdrawal of consent (attempts should be made to clarify, with the patient, if withdrawal is specific to study participation, or if it applies to data collection as well). Note: patients lost to follow up (defined as no contact > 60 days after last on-study contact and at least 3 attempts) are considered to have withdrawn study participation consent. Data collection is permissible. Date of last contact will be recorded as the withdrawal date.
- Pregnancy
- Oncoceutics' decision to forgo further drug development of ONC201

The reason for study removal and the date the patient was removed must be documented in the CRF.

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 he 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.

5.6 Dose Limiting Toxicity (DLT) definition

Toxicity will be evaluated according to the NCI CTCAE, version 4.03. The DLT safety observation window is defined as the first 3 weeks (one cycle). A DLT will be defined as any of the following AEs, occurring within the first 21 days of dosing and considered possibly related (except where defined) to ONC201:

Hematologic:

- Grade 4 neutropenia that persists for >7 consecutive days
- Febrile neutropenia (defined as neutropenia ≥ Grade 3 and a body temperature 38.5°C)
- Grade ≥ 3 neutropenic infection
- Grade 4 thrombocytopenia (platelets <25,000 cells/mm3) or Grade ≥ 3 thrombocytopenia with bleeding

Nonhematologic:

- Any other Grade ≥ 3 toxicity not classified under CTCAE blood or bone marrow with the exception of nausea, vomiting, or diarrhea. Grade 3 nausea or vomiting that persists for 5 days and is not controlled with standard antiemetic therapy will be considered a DLT.
- Alopecia is not a DLT
- Any AE leading to inability to complete planned study drug during the DLT window should be considered a DLT

Although toxicities may be observed at any point during treatment, only those occurring during the defined DLT observation window of treatment (1 cycle) that are considered DLTs will guide dose escalation decisions, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities, and all toxicities, including those occurring in beyond the DLT observation window will be monitored.

6 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 (Table 6.1) for adverse events that are attributable to study drug, including: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. 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.

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), including Nausea, Diarrhea, Neutropenia, Thrombocytopenia, 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. For first instance, if resolved to < Grade 2 within 21 days resume dosing at 500mg ONC201 and 8mg dexamethasone. For second instance, if resolved to < Grade 2 within 21 days resume dosing at 8mg dexamethasone and 375mg ONC201.**
*Patients requiring a delay of >21 days weeks should go off protocol 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 21 days, the interval for testing may be reduced after consultation and written approval by the Overall Principal Investigator (or his designee).

For holds for reasons other than treatment related toxicities, if the participant does not meet criteria to resume treatment within 6 weeks of the event precipitating the hold, the study

agent(s) may be restarted with approval from the overall Principal Investigator or designee, as long as there has been no significant evidence of disease progression (e.g., by clinical findings, symptoms, tumor markers) during the treatment interruption.

6.1 Concomitant Medications

6.1.1 Drug Interactions

No formal metabolic or 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 not be used on study. Concomitant medications that have risk of Torsades de Pointes are also not allowed.

6.1.2 Corticosteroids

Dexamethasone will be given to all patients per study protocol. Additional steroids will be restricted to physiologic replacement or less for those in which it is clinically indicated.

Use of non-systemic steroid use is permitted (e.g. cream, lotion, inhalers).

6.1.3 Anti-emetic Therapy

There are no restrictions on use of antiemetic therapy for this trial. Premedications to prevent emerging toxicities are permitted as long as their use does not conflict with other guidelines in this protocol.

6.1.4 Other Anticancer or Experimental Drugs

Treatment with other anticancer or experimental drugs is not permitted for patients treated on this protocol. Exceptions include use of LHRH, and octreotide.

6.1.5 Hematopoietic Growth Factors

The use of any growth factor is not permitted for patients during the DLT window, unless it's use is deemed medically necessary by the treating physician secondary to an emerging toxicity. In this situation, only G-CSF is permitted for neutropenic fever or grade 4 neutropenia > 7 days duration, if the investigator feels such treatment would be in the patient's best interest. Use of growth factors outside of the DLT window must follow institutional and ASCO guidelines. In situations where G-CSF is felt to be warranted, pegylated G-CSF should only be used if the study drug dosing interval is 2 weeks or greater. G-CSF must be used if the study drug dosing interval is 1 week.

The use of erythropoietin growth factor is generally discouraged. Use of erythropoietin must follow institutional and ASCO guidelines. The use of a thrombopoietin agonist is not permitted.

6.2 Palliative and Supportive Care

All palliative care necessary for optimal care of the patient should be provided. Investigational drug must be held during radiotherapy and for 1 week afterwards. If possible, the investigational drug should be held for 1 week prior to the administration of palliative radiotherapy if possible. It is not known if ONC201 acts as a radiosensitizer or if this would lead to increased toxicity. However, the potential for ONC201 to act as a radiosensitizer exists. ONC201 should be held for at least one week prior to any elective surgery.

7 STUDY PROCEDURES

Note that hematology, blood chemistry, and urinalysis, below, refers to any biologic sampling done for safety or efficacy testing, as detailed in the Schedule of Activities. For example, patients with multiple myeloma may undergo a 24-hour urine collection but this is not explicitly defined in the text below. The Schedule of Activities take precedence over text in this section.

7.1 Baseline

The following procedures/assessments must be performed within 28 days prior to the first dose of ONC201.

- Patient signature on informed consent form
- Medical history, including tumor history, history of other disease processes (active or resolved), concomitant illnesses, and demographics.
- Tumor assessment.

The following procedures/assessments must be performed within 28 days prior to the first dose of ONC201.

- Baseline signs and symptoms
- Vital signs
- Height
- Weight
- Physical exam
- ECOG performance status
- Hematology, blood chemistry, coagulation, urinalysis and per SoA
- Pregnancy test (serum or urine), if applicable
- Triplicate EKG (12 leads)
- Concomitant medications

Following successful completion of the baseline assessments and confirmation of eligibility patients may be enrolled.

7.2 Trials Period

The following procedures/assessments will be performed on the days specified in the Schedule of Activities:

- Vital signs
- Weight
- ECOG performance status
- Physical exam
- Hematology, blood chemistry, coagulation, urinalysis, and per SoA
- Triplicate EKG (12 leads)
- Study drug compliance
- Adverse events
- Drug compliance
- Concomitant medications
- Tumor assessment: at the end of every even cycle (e.g., Cycles 2, 4, 6)
- Blood draws for PK/PD
- Urine collection

7.3 Treatment

ONC201 will be orally administered at 625mg weekly day 1, day 8, and day 15 of each treatment cycle (21 days). Dexamethasone will be administered at the indicated dose on each day that ONC201 is administered in each treatment cycle (day 1, day 8, and day 15). Administration of dexamethasone is recommended approximately 6 hours (+ 2 hours) after ONC201.

7.4 End of Treatment Visit

A final visit (“Follow Up”) will occur for all patients when disease progression is documented or subsequent anticancer therapy is initiated or the patient is withdrawn from treatment for any other reason.

The following procedures/assessments will be carried out as described in the Schedule of Activities table and unless performed in the previous week. Every effort should be made to have a final tumor assessment.

- Vital signs
- Weight
- ECOG performance status
- Triplicate EKG (12 leads)
- Hematology, blood chemistry, coagulation, urinalysis and per SoA
- Tumor assessment, unless carried out in the previous 6 weeks
- Adverse events
- Concomitant medications

7.5 Follow-up Visit

Safety follow up will continue in all patients for 28 days after the last dose of treatment. For those patients who have discontinued study treatment for reasons other than disease progression, all tumor assessments should be repeated every 6 weeks until disease progression or another antitumor therapy is initiated.

7.6 Patient Withdrawal

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment ≥ 14 days or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance with protocol requirements (determined via meeting with PI, applicable Sub-I, clinical research coordinator, and patient)
- Unacceptable adverse event(s). Note, a DLT in and of itself may not be an unacceptable adverse event. However, any grade 4 study-drug related AE is unacceptable and will lead to withdraw. The investigator will use his/her opinion, in consultation with the PI, to determine if a study-drug related AE is unacceptable, acceptable, or clinically insignificant (also acceptable).
- Withdrawal of consent (attempts should be made to clarify, with the patient, if withdrawal is specific to study participation, or if it applies to data collection as well). Note: patients lost to follow up (defined as no contact > 60 days after last on-study contact and at least 3 attempts) are considered to have withdrawn study participation consent. Data collection is permissible. Date of last contact will be recorded as the withdrawal date.
- Pregnancy
- Oncoceutics' decision to forgo further drug development of ONC201

8 ASSESSMENTS

8.1 Safety Evaluations

Safety assessments include collection of AEs, SAEs, and safety laboratory. Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), timing, seriousness, and relatedness.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

The minimum requested lab data includes:

Table 7.1: Laboratory Tests Required (All patients)

Hematology	Blood Chemistry	Urinalysis	Coagulation tests
White Blood Cell Count (WBC)	Glucose	pH	Activated partial thromboplastin time (APTT)
Absolute Neutrophil Count (ANC)	BUN	Specific gravity	Prothrombin time
Platelet count	Creatinine	Protein	
Hemoglobin	Albumin	Glucose	
WBC differential count	AST/ALT	Ketones	
	Total Bilirubin	Blood	
	Alkaline phosphatase	Leukocyte esterase	
	LDH	Nitrates	
	Sodium		
	Magnesium		
	Potassium		
	Calcium		
	Phosphate		
	Uric Acid		

Investigators may order additional blood tests for planning treatment administrations, dose modification, or further evaluation of adverse events.

Additional assessments are defined in the Schedule of Activities table.

8.2 Efficacy Evaluations

Assessment of response will be made using the International Myeloma Working Group response criteria (Palumbo et al, 2014). All patients' files and radiologic images must be available for source verification.

Imaging may include chest, abdomen and pelvis CT or MRI or PET/CT scans (when applicable); brain CT or MRI scan for patients with known CNS involvement; bone scan and/or bone x-rays for patients with lytic bone lesions, if applicable.

Tumor assessments conducted at baseline, at the end of every other cycle, whenever disease progression is suspected (e.g., symptomatic deterioration), and at the time of withdrawal from the study (if not done in the previous 6 weeks).

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Assuming a background ORR of 10%, if the ORR 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 an objective response. Enrollment of 30 patients will yield 84% power to detect a 20% difference at an alpha level of 0.05 (one-sided).

8.3 Correlative studies

8.3.1 Background
Molecular markers involved in the molecular mechanism of ONC201 will be assessed on available tumor and serum specimens. Urine samples may be used to evaluate the excretion of ONC201 or its metabolites.

8.3.2 Biomarkers
Prolactin and other proteins will be measured in serum as pharmacodynamic markers. One red-top tube (without anti-coagulant) of blood will be collected at the following time points: Baseline and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8; Cycle 1 Day 15. An additional 1 tube of 5mL of blood will also be collected on the day of drug administration (pre-dose) on cycles 2, cycle 3 and every odd cycle beyond cycle 3 (day 1 of each cycle). For patients with archival specimens, genomic analysis may also be investigated to determine if a mutation signature profile can help predict safety and/or efficacy

8.3.3 ONC201 Plasma Concentration
The plasma obtained prior to the isolation of PBMCs (see Section 8.3.4) will be used to determine the concentration of ONC201. No additional blood samples will be collected from the patient for these studies. These samples will be used to approximate the Cmax of ONC201 based on its pharmacokinetic profile.

8.3.4 Blood for Immune Cell Studies
Peripheral blood mononuclear cells (PBMCs) will be harvested and investigated for effects of ONC201 on the immune system. One EDTA tube of blood will be collected at the same time points as the red-top tubes are collected: Baseline and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8; Cycle 1 Day 15; pre-dose for the first day

of cycle 2 and beyond (day 1 of each cycle). Blood will also be collected at the follow-up visit at the end of treatment, for correlative studies.

Immune cytokines and effectors will be assessed on serum samples obtained for pharmacodynamic analyses. No additional blood samples will be collected from the patient for these studies.

8.3.5 Urine Collection for ONC201 metabolism Studies

An aliquot of the 24 hour baseline urine collection will be needed. The Cycle 1 Day 1 - 24 hour urine collection will be moved to Cycle 1 Day 2. The patients will collect urine in the clinic on Cycle 1 Day 1, starting after taking the first dose of ONC201. The urine will be stored at the site, and the number of hours for this portion of the collection and the volume will be recorded. The patients need to remain in the clinic until the 6 hour PK sample is drawn. The patients will go home with empty bottles provided by the site to finish collecting the 24 hour urine sample and the patient will be told the time of completion and will return the next day. The number of hours for this portion of the collection and the volume will be recorded as well, and 100mL aliquots from both samples will be frozen and transported to Biorepository. On Cycle 1 Day 2 and Day 3, there will be a spot urine.

8.4 EKG Assessments

Triplicate 12-lead EKGs will be performed per the Schedule of Activities and include baseline, cycle 1 day 1, cycle 1 day 15 and cycle 2 day 1, and cycle 2 day 15. Cycle 1 day 1 and cycle 2 day 1 will be obtained at 2 hours (+15 minutes) post-dose. Cycle 1 day 15 and cycle 2 day 15 will be taken pre-dose. Electrocardiogram assessments are to be performed after the measurement of vital signs, with the patient supine and rested for 5 minutes, and before any closely timed blood collection. Two – 5 minutes should lapse between each EKG assessment. The dates and exact times of EKG recordings will be recorded. Any findings from EKGs collected after initiation of study treatment will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

8.5 Concomitant Medications

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the CRF from screening through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

9 ADVERSE EVENT REPORTING

9.1 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 study regulatory file.

The principal investigator has the obligation to report all serious adverse events to Oncoceutics (the Sponsor).

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study 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 study discontinuation need only be reported if a relationship to ONC201 study 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.

9.2 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 clinical trial, i.e., prior to undergoing any trial-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 trial treatment through last patient visit.

If a subject 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.

9.3 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 under trial 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

9.4 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

9.5 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 trial (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 trial 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 9.7, 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.

The Sponsor will notify the FDA of any adverse experience associated with the use of the drug that is both serious and unexpected, as soon as possible and in no event later than 15 calendar days after the PI’s discovery of the event. Notification may be submitted to the Sponsor on a MedWatch Form FDA 3500A http://www.fda.gov/medwatch/safety/3500a.pdf.

The PI shall also notify the Sponsor of any unexpected fatal or life-threatening experiences associated with the use of the drug, as soon as possible but no later than 7 calendar days from the PI's discovery of the event information.

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 a MedWatch form.

9.6 Hospitalization

Adverse events reported from clinical trials 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 during a clinical trial (e.g., for a procedure required by
- the trial 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.

9.7 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.

9.8 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 trial records.

In addition, if the investigator determines a serious adverse event is associated with trial 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.

9.9 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 study, she must inform the investigator immediately and permanently discontinue study drug. Oncoceutics must be immediately (with 24 hours of awareness) be contacted. The pregnancy must be followed for the final pregnancy outcome.

If any trial patient or trial patient's partner becomes or is found to be pregnant during the trial 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 study 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.

9.10 Withdrawal Due to Adverse Events

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page. When a patient withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

9.11 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events.

9.12 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.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

9.12.1 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Oncoceutics is to 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.

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 trial 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.

9.12.2 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 subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

A. Subjects with AST or ALT baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal concurrent with a total bilirubin ≥2 times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase · 2times the upper limit of normal or not available.
B. Subjects with pre-existing AST or ALT baseline values above the normal range who subsequently present with AST or ALT ≥2 times the baseline values and ≥3 times the upper limit of normal, or ≥8 times the upper limit of normal (whichever is smaller) concurrent with a total bilirubin of ≥2 times the upper limit of normal and increased by one upper limit of normal over baseline or >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 subject 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 subject, 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.

9.12.3 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRF.

10 DATA ANALYSIS/STATISTICAL METHODS

10.1 Efficacy Evaluation

All patients who have received a minimum of 2 cycles of study treatment had baseline assessments and at least one on-study tumor assessment following treatment will be considered evaluable for response.

Objective Response Rate (ORR) is defined as the proportion of patients with a Complete (CR) or Partial Response (PR) relative to the total number of evaluable patients. Responses will be defined according to the International Myeloma Working Group response criteria (see Appendix C: Multiple Myeloma Disease Tracking for Myeloma Worksheet).

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or the withdrawal from the study. Stable disease will be considered the best response when observed at least after two months from baseline.

Tumor responses will be analyzed in a descriptive manner. The number and percentage of objective response (CR+PR) will be tabulated by dose level. An ORR may be summarized for the RP2D expansion cohort with the corresponding 95% exact confidence interval.

10.2 Futility Analysis

A Bayesian method by Thall et al (1995) will be used for futility monitoring in Phase 2 of the study. The trial will be stopped early if Pr (ORR < 0.1 |data)>0.95. That is, the trial will be stopped early if there is more than a 95% probability that the ORR is lower than 10%. We assume that ORR follows a prior distribution of beta (0.1, 0.9).

The futility rules will be implemented once the first 12 patients have been enrolled in Phase 2. The corresponding stopping boundaries are listed in the following table 10.1. For example, if there are no responses in the first 12 patients enrolled in Phase 2, the trial will be terminated early due to futility. Multc Lean software V2.1 was used for the design. If the trial continues until 20 additional patients are evaluated, and 3 responses are observed among the 26 patients, then the 95% credible interval for the response rate would be (2.6%, 25.7%).

Table 10.1: Stopping boundaries for futility monitoring

# Patients (inclusive)	Stop the trial if there are this many responses total:
	# responders (inclusive)
1-11	Never stop with this many patients
12-23	0
24-25	0-1
26	Reach maximum number of patients, always stop

10.3 Early Stopping Rules for Safety/adverse events:

Adverse events will be assessed continuously throughout the study. During evaluation of the first cohort of 12 eligible patients, if 4 patients have to discontinue the study drug due to treatment-related adverse events, the study will be interrupted for consideration of dose reduction or termination. If 6 of a total of 26 eligible patients have to discontinue the study drug due to treatment-related adverse events the study will be suspended and early termination for excess toxicity will be considered after careful investigation of the causes of the higher than expected toxicities. Once the cause of the higher than anticipated toxicities has been determined, the study team will confer with the FCCC DSMC and IRB to make a determination whether accrual can be resumed or the study will be terminated early. The chance of early termination with a true toxicity of 30% is 51%. The chance of early termination in error (when true toxicity is 5%) is 0.2%. The overall study power is 85% (for detection of overly toxic treatment) and has type I error of 0.3%.

11 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Oncoceutics (or its representatives) will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will also review source documents to confirm that the data recorded on CRFs is accurate. Direct access to source documents to perform this verification will be provided.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each enrolled patient. The completed original CRFs are the sole property of FCCC and Oncoceutics, and are subject to review by appropriate regulatory authorities.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the physician's patient records maintained at the trial site.

12.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records will be retained by the investigator according to ICH and local regulations.

If the investigator relocates, retires, or for any reason withdraws from the trial, the trial records must be transferred to an acceptable designee, such as another investigator or another institution.

13 ETHICS

13.1 Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, from the IRB.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB in writing within 5 working days after the implementation.

13.2 Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

13.3 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 (ICF) must be approved by the IRB and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

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

14 DEFINITION OF END OF TRIAL

The end of trial is defined as the time when enrollment is completed according to protocol planned sample size, and assessment and requirements are completed as per protocol, and the stated objectives of the trial are achieved.

15 DISCONTINUATION CRITERIA

Premature termination of this clinical trial 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.

16 PUBLICATION OF TRIAL RESULTS

All information regarding ONC201 supplied by Oncoceutics to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Oncoceutics. It is understood that there is an obligation to provide Oncoceutics with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of ONC201 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required. Upon completion of the clinical study and evaluation of results by Oncoceutics, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising

Oncoceutics employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience gained during the conduct of the study.

A prepublication manuscript or abstract is to be provided to Oncoceutics a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Oncoceutics of the notification, Oncoceutics shall inform the study center whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Oncoceutics' receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.
- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Oncoceutics' request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Oncoceutics.

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18 APPENDIX:

18.1 Appendix A: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CNS	Central Nervous System
C_{max}	Maximum plasma Concentration
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FCCC	Fox Chase Cancer Center
H&P	History and Physical
ITP	Investigational Therapeutic Protocol
ITT	Intention to Treat
LDH	Lactate Dehydrogenase
MAD	Maximally Administered Dose
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
PD	Pharmacodynamic
PK	Pharmacokinetic
PS	Performance Status
RP2D	Recommended Phase 2 Dose
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of Activities
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential

18.2 Appendix B: Performance Status

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	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.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

18.3 Appendix C: Multiple Myeloma Disease Tracking

Multiple Myeloma Disease Status Tracking

Monoclonal Protein: IgA IgD IgE IgG IgM **Light Chain:** Kappa(κ) Lambda(λ)

	Values							Yes/No	
Date	Immuno-fixation (Serum)	Immuno-fixation (Urine)	SPEP	UPEP	24-Hour Urine	κ/λ ratio	% Plasma Cells in BM	Plasma-cytomas?	Lytic Lesions?