Phase 1/2 Study of Oral ONC201 in Patients with Relapsed/Refractory Non-Hodgkin's Lymphoma

Protocol # 2014-0630

November 13, 2018

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1 BACKGROUND

1.1 DEFINITION AND CLINIC COURSE OF MCL

Mantle cell lymphoma (MCL) is an aggressive and distinct type of B-cell non-Hodgkin lymphoma (NHL) that is relatively rare, accounting for ~4–8 % of adult NHL (Weisenburger et al., 1982). This disease affects primarily the elderly population, with a median age of 68 years at diagnosis, and is more prevalent in men and Caucasians (Zhou et al., 2008). The median overall survival in this setting is under 5 years, though survival has improved drastically in recent decades due to the emergence of new therapies (Herrmann et al., 2009).

The World Health Organization (WHO) classifies MCL on the basis of clinical, histopathological, immunological, and cytogenetic or molecular data (Swerdlow et al., 2008). The genetic characteristic of MCL is the t(11;14)(q13;q32) translocation that juxtaposes the immunoglobulin heavy chain variable region (IGVH) gene on 14q32 to the CCND1 gene on 11q13, resulting in the overexpression of cyclin D1 (Jares et al., 2007). There is a small subset of cyclin D1-negative MCL tumor, but they are morphologically, immunophenotypically, and by global expression profile indistinguishable from conventional MCL. These CCND1-negative tumors typically express SOX11 that may be used as a diagnostic for these patients (Rosenwald et al., 2003; Salaverria et al., 2013).

MCL is treated with chemotherapy regimens that are used to treat other subtypes of lymphomas: alkylating agents, fludarabine, and bendamustine. Rituximab is an anti-CD20 antibody that is commonly combined in most regimens. A widely used regimen is the combination of rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) (Khouri et al., 2005; Romaguera et al., 2005). This regimen resulted in a median time to treatment failure of 4.6 years, although toxicities were significant and caused ~30% of patients to discontinue therapy prior to completing cycles. Maintenance therapy typically uses rituximab based on efficacy benefits observed in small studies (Forstpointner et al., 2006, Kahl et al., 2006).

After the first relapse, the prognosis is poor, with a median survival of approximately 1–2 years (Khouri et al., 2003; Hiddemann et al., 1998). Bortezomib is a proteasome inhibitor approved by the US FDA to treat relapsed/refractory MCL based on the data from a multicenter Phase 2 study (Fisher et al., 2006; Goy et al., 2009). This study confirmed the single-agent activity of bortezomib in patients with relapsed or refractory MCL who have received at least one prior therapy. The overall response rate was 33%, including an 8% complete response (CR). The median time to progression was 6.7 months, and the median overall survival was 23.5 months. Recently, ibrutinib was approved in relapsed/refractory MCL based on a response rate of 68%, with a complete response rate of 21% and a partial response rate of 47% (Wang et al, 2013). Prior bortezomib therapy did not alter the clinical efficacy of ibrutinib. Despite the emergence of these new treatment options, therapy resistance is very common in MCL (Leonard et al., 2001) and additional treatment options are needed in this setting due to the poor prognosis and difficulties with tolerating therapies in this aging population.

1.2 DIFFUSE LARGE B-CELL LYMPHOMA AND FOLLICULAR LOW GRADE LYMPHOMA

Diffuse large B cell lymphomas (DLBCLs) are the most common subtype of NHL, representing 30-40% of adult NHLs. Approximately 50-60% of patients with DLBCL maintain complete remission after first-line therapy. However, 30-40% relapse; 10% have refractory disease and have a poor prognosis, with an overall survival of 3-4 months without treatment (Perry et al., 1998; Fisher et al., 1993; Pfreundschuh et al., 2006). Prognostic factors include: time to relapse, relapsed or refractory disease, Age Adjusted International Prognostic Factors Index, and rituximab naïve status (Vellenga et al., 2008; Campo et al., 2011; Kewalramani et al., 2004; Hamlin et al., 2003; Martín et al., 2008).

Improving survival in DLBCL is expected to require optimization of therapy in NHL, and the identification of new therapies with compelling efficacy and an acceptable safety profile in combination with other chemotherapies.

Follicular low grade lymphoma is the second most common subtype of NHL and accounts for 20% of NHL. Most patients present with advanced stage IV disease; although more indolent in behavior, it is still incurable. As quality of life becomes even more relevant in this subtype, and since current chemotherapy combinations carry with them known toxicity, identification of new drugs which are efficacious and have new mechanisms of action and a very low toxicity profile are desirable (Kahl BS et al. Blood. 2016)

1.3 INVESTIGATIONAL AGENT ONC201

ONC201 (TIC10) is a first-in-class small molecule that induces ER stress and inactivates the Ras effector target kinases, Akt and ERK, selectively in tumor, but not normal, cells to safely trigger cancer cell death (Allen et al., 2013).

1.4 NONCLINICAL PHARMACOLOGY

ONC201 is a first-in-class small molecule targeted anticancer compound under development by Oncoceutics to treat advanced cancer. ONC201 is a stable, water soluble, orally active, and blood brain barrier-penetrable compound that has demonstrated p53-independent anticancer activity in many preclinical models that include glioblastoma, breast cancer, colon cancer, lung cancer, lymphoma, and others. ONC201 kills cancer cells while sparing normal cells by inducing ER stress and inactivating the prosurvival kinases Akt and ERK in tumor, but not normal cells, to trigger antitumor effects such as apoptosis. In normal cells, only a partial and transient inactivation of one of the pathways is observed that does not induce cell death. The safety profile of ONC201 in GLP safety studies is consistent with this differential activity of ONC201 in tumor versus normal cells. Dual inactivation of Akt and ERK by ONC201 is sustained in tumor but not normal cells, is maintained in the presence of upstream stimuli such as ligands or mutations, and allows for broad-spectrum antitumor activity despite cancer cell resistance to chemotherapy, radiation, and targeted therapy. ONC201 prolongs survival and shrinks tumors in a variety of preclinical models, including

highly mutated and refractory cancer patient samples and cancer cell lines in vitro and in vivo.

The profile of ONC201 is well suited for an oncology product: efficacious with infrequent administration, broad-spectrum activity independent of mutations, orally active, compelling safety profile, combines synergistically and safely with many approved therapies, highly active by employing a combination of established anti-tumor/pro-apoptotic pathways, highly stable, water soluble, and penetrates the blood-brain barrier. The 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 efficacy of ONC201 has been consistently demonstrated in >80 in vitro models and 16 in vivo experiments (subcutaneous, orthotopic, and transgenic) and confirmed by multiple leading cancer research institutions.

1.5 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 displays single agent anti-tumor effects (Figure 1.1) in subcutaneous and orthotopic colon cancer, subcutaneous triple negative breast cancer, subcutaneous non-small cell lung cancer, subcutaneous and orthotopic intracranial glioblastoma, and immunocompetent lymphoma transgenic mouse models. ONC201 also cooperates extensively with paclitaxel, docetaxel, sorafenib, and bevacizumab.

ONC201 has demonstrated striking induction of apoptosis in ex vivo refractory cancer specimens harvested from patients with hematological malignancies. Compelling cytotoxic activity has been documented MCL patient samples, including tumors with p53 mutations and resistance to standard-of-care agents, such as the recently approved agent ibrutinib. Below reviews preclinical studies with ONC201 in MCL that warrant the clinical evaluation of ONC201 as a novel treatment in advanced NHL.

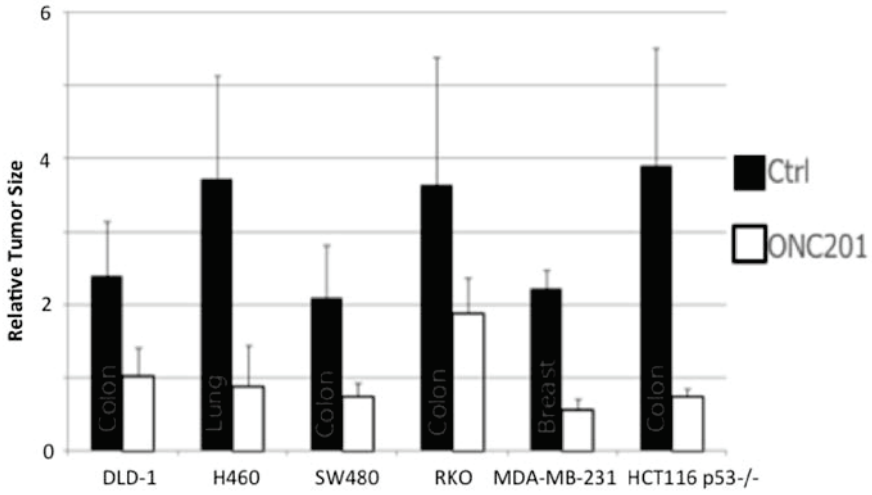


Figure 1.1. ONC201 antitumor activity in subcutaneous xenografts. Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and is relative to the tumor size on the day of administration.

ONC201 induced potent antitumor effects in several mantle cell lymphoma models lymphoma cell lines and patient samples (Ishizawa J. 2014). Induction of apoptosis in MCL cell lines has been documented, which was particularly pronounced in the cell lines with mutant p53 (Figure 1.2). Despite this observation, the activity of ONC201 in MCL cell lines was p53-independent, which is in accordance with prior reports in CRC and GBM (Allen et al, 2013) (Figure 1.3). Importantly, the compelling cytotoxicity exerted by ONC201 was not accompanied by evidence of genotoxic stress, which bodes well for its safety (Figure 1.4).

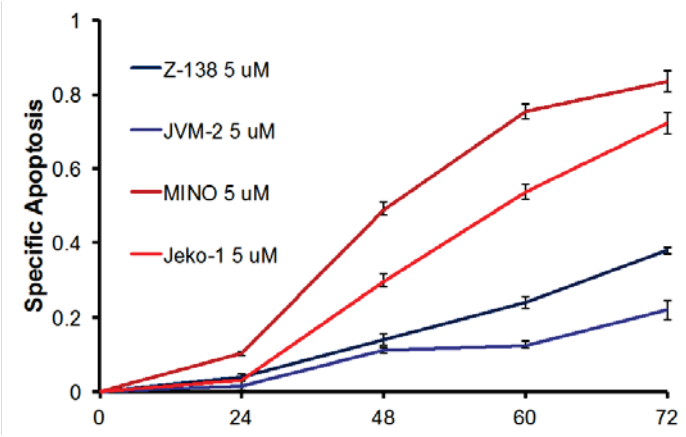


Figure 1.2. Induction of apoptosis by ONC201 in indicated MCL cell lines as a time course following ONC201 treatment (5uM). (Ishizawa J and Andreeff M, unpublished data, 2014.)

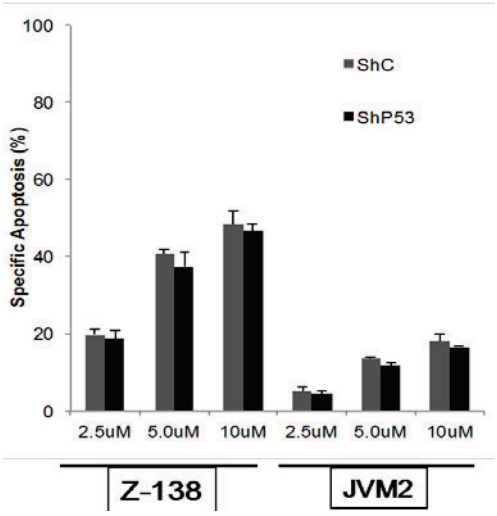


Figure 1.3. Induction of apoptosis by ONC201 in indicated MCL cell lines. The dose of ONC201 is indicated in the plot (72 hrs). (Ishizawa J and Andreeff M, unpublished data, 2014.)

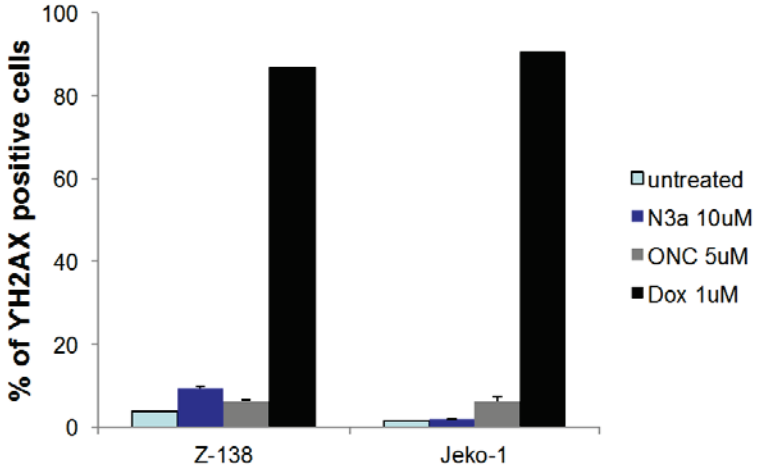


Figure 1.4. YH2AX levels in MCL cell lines following treatment with ONC201 or comparator compounds. Drug incubation for 36 hours with ONC201 (ONC), 24 hours with Nutlin 3a (N3a), or 6 hours with doxorubicin (Dox) at indicated concentrations. (Ishizawa J and Andreeff M, unpublished data, 2014.)

In addition to activity in MCL cell lines, ONC201 also has proven highly effective against primary specimens, including induction of apoptosis in newly diagnosed as well as refractory MCL (Figure 1.5). These samples also included documentation of cytotoxic activity against blastic MCL tumors, which harbor mutant p53, as well as activity in ibrutinib-refractory MCL samples (Figure 1.6). The robust induction of apoptosis where such a clinically effective agent fails demonstrates the strong efficacy of the molecule, especially given the absence of bone marrow toxicity that usually plagues this setting. The compelling in vitro data in NHL is complemented by prior studies with ONC201 in the Eu-myc transgenic mouse models where mice develop spontaneously develop myc-driven B-cell lymphomas. Oral ONC201 administered weekly for 4 weeks resulted in all mice surviving while on drug and a total extension of 4 weeks in overall survival that was statistically significant without apparent toxicity (Figure 1.7). These studies cumulatively indicate that ONC201 is a highly effective monoagent in preclinical models of advanced NHL.

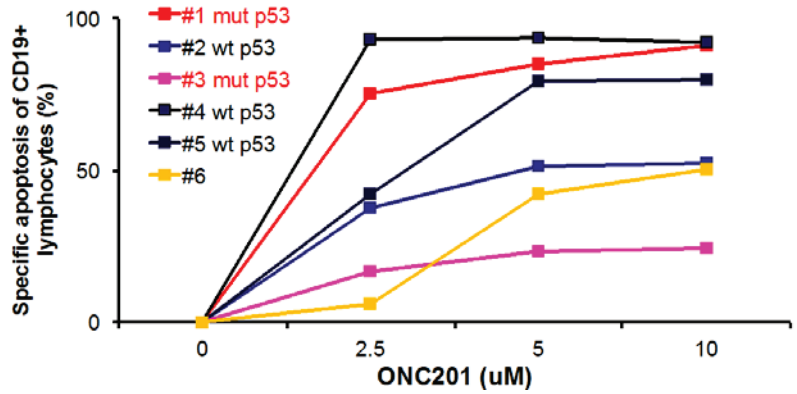


Figure 1.5. Induction of specific apoptosis in primary MCL samples following ONC201 treatment at indicated concentrations (72 hrs). P53 mutation status is indicated in the figure key. (Ishizawa J and Andreeff M, unpublished data, 2014.)

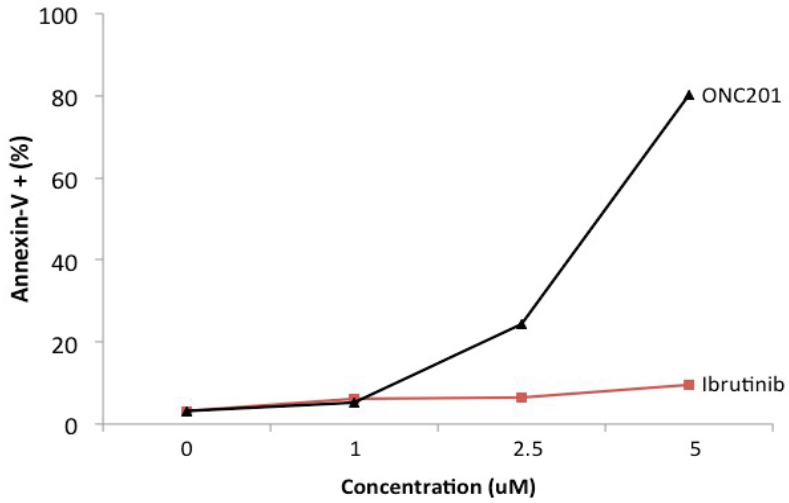


Figure 1.6. Primary refractory MCL patient sample treated with ONC201 or ibrutinib at indicated dose (72 hrs). (Ishizawa J and Andreeff M, unpublished data, 2014.)

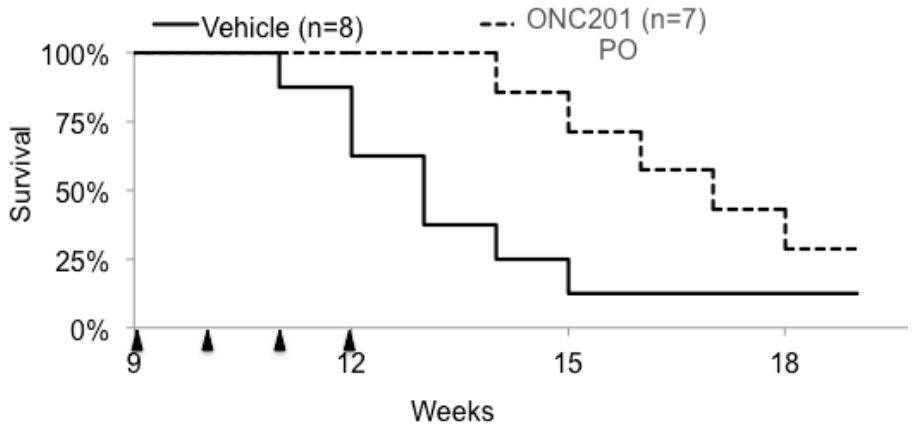


Figure 1.7. ONC201 prolongs the survival of transgenic mice with lymphoma. Overall survival of Eμ-myc treated once a week during weeks 9-12 with ONC201 (PO, qwk). P=.00789 determined by log-rank test

1.6 MECHANISM OF ACTION

ONC201 directly antagonizes DRD2 to activate the integrated stress response (ISR) that attenuates protein translation and activates ATF4, which causes induction of genes that lead to apoptosis (Figure 1.8). ATF4 and CHOP also downregulate Akt and ERK activity that cooperatively induce complementary downstream apoptotic effects. Studies have shown that ONC201 does not inactivate eIF2-alpha through PERK, which is activated by ER stress. 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. This mechanism of action explains the pronounced sensitivity of ONC201 in B cell malignancies that are particularly sensitive to the integrated stress response.

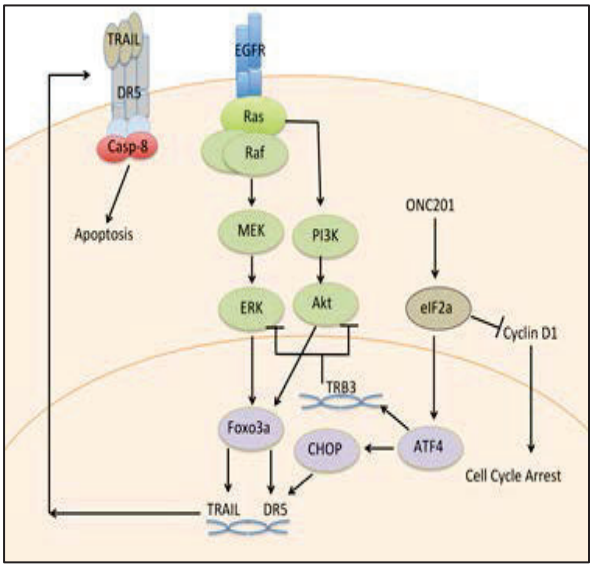


Figure 1.8 Proposed model of ONC201 in tumor cells.

1. 7 PRECLINICAL ACTIVITY

1.7.1 IN VITRO MONOAGENT

ONC201 caused a dose-dependent decrease in the cell viability and colony formation capacity of human cancer cell lines. ONC201 induced Sub-G1 content in the TRAIL-sensitive HCT116 cells at

5-10 μM doses in a p53-independent and Bax-dependent manner as expected. The in vitro activity of ONC201 was confirmed in a variety of solid human tumor cell lines that represented breast, colon, liver, ovarian, and prostate cancer with consistent activity observed in the 2-5 μM range). This potency in cell-based assays is comparable to a majority of FDA-approved target anticancer agents such as sorafenib, sunitinib, lapatinib, nilotinib, gefitinib, erlotinib, and imatinib. ONC201 had similar in vitro activity in a panel of lymphoma cell lines representing Burkitt's lymphoma, non-Hodgkin's lymphoma, mantle cell lymphoma, leukemic mantle cell lymphoma, and centroblastic diffuse lymphoma.

In addition to observing reduction in cancer cell viability, ONC201 induced apoptosis in several human cancer cell lines. ONC201 caused a large increase in the amount of markers of apoptosis such as Sub-G1 content, cleaved caspase-3, and blockade of Sub-G1 with zVAD-fmk in several cancer cell lines. zVAD-fmk is a pan-caspase apoptosis inhibitor that functions by binding to the active site in caspases that carry out proteolysis by mimicking its substrate.
ONC201 demonstrated p53-independent activity in human GBM cell lines in the low micromolar range. ONC201 exerted a strong cytotoxic effect, unlike temozolomide, against tumor cells isolated from a freshly resected GBM with an oligodendroglial component that was previously resected and irradiated. Corroborating observations by external investigators have demonstrated the compelling monoagent efficacy of ONC201 in radio- and chemo-resistant GBM cell lines and 3D neurosphere cultures. Examples of other compelling efficacy studies from external investigators include monoagent activity in refractory blastic mantle cell lymphoma patient samples, vemurafenib- resistant melanoma, and head and neck squamous cell carcinoma.

1.7.2 EFFECTS ON NORMAL CELLS

ONC201 does not highly impact the cell cycle profile or gross culture of normal human fibroblasts at doses that induce cell death in human cancer cells. ONC201 treatment eradicated the cancer cell population while sparing the normal cells in a co-culture experiment. Comparing ONC201 dose-response relationships between tumor and normal cell lines revealed a similar inflection point at ~5μM that subsequently saturated in all tested cell lines. However, ONC201 saturated efficacy at a much lower level (<25% reduction in cell viability) than observed in normal cells (>70%). This observation was in contrast to the positive control, doxorubicin, which results in massive cell death of normal cells. To ascertain if this reduction in cell viability was associated with a reduction in proliferation or an increase in cell death, we investigated cell cycle profiles of normal cells. ONC201 treatment did not cause any appreciable levels of cell death in normal cells, but drastically increased cell death in tumor cells (Figure 1.9).

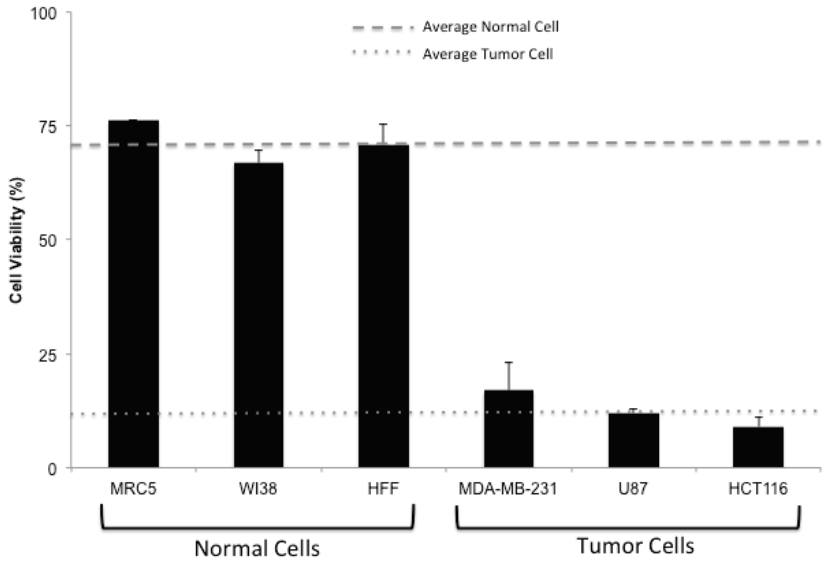


Figure 1.9. ONC201 effects on proliferation and cell death in normal and tumor cells. Cell viability of normal and tumor cell lines following ONC201 treatment for 72 hr (10 uM, n=3).

With the observation that ONC201 slightly reduces cell viability in normal cells, we next assayed whether this was a transient phenomenon. We found that removing ONC201 at the end of a 72-hour incubation period resulted in a time-dependent complete recovery that was evident 24 hours later. This is promising as ONC201 is largely cleared from the body in rats and dogs within 24 hours. We investigated the possibility that the difference between tumor and normal cells is simply a function of proliferation. Examining this relationship revealed no obvious correlation between the ability of ONC201 to reduce cell viability and the doubling rate of the cell line. These results suggest that ONC201 induces cell death in tumor but not normal cells; that ONC201 can cause a slight reduction in normal cell proliferation that is transient and reversible; and, that ONC201 activity does not appear to be overtly related to proliferation rate.

ONC201 treatment results in a mild inhibition of pERK and its phosphorylation site on Foxo3a (S294) in WI-38 normal fibroblasts. A very slight effect on Akt phosphorylation was noted, though this did not correlate with changes in Foxo3a S253 phosphorylation under these conditions, which is the site on Fox3a that is phosphorylated by Akt. In HFF cells, ONC201 results in decreased pAkt but not pERK, with similar observations on their respective Foxo3a phosphorylation sites. ONC201 upregulates surface TRAIL in tumor and normal cells, though to a lesser magnitude in normal cells. Interestingly, DR5 induction was absent in normal fibroblasts as opposed to tumor cells that boosted production of the death receptor in response to ONC201. Doxorubicin was also capable of boosting surface TRAIL as well as DR5 proteins at similar magnitudes in tumor and in normal cells, demonstrating no appreciable differential activity between tumor and normal cells. Investigating the effects of ONC201 and doxorubicin on surface TRAIL and DR5 in other normal fibroblasts confirmed these observations. A slight induction over basal levels of DR5 in ONC201-treated WI-38 cells was observed, although the increased levels were much lower than induction by doxorubicin treatment. These results suggest that the therapeutic index associated with ONC201 is likely due to the general absence of DR5 induction as well as absence of dual Akt/MEK inactivation in normal

cells.

1.7.3 IN VIVO MONOAGENT

The efficacy of ONC201 has been evaluated in a number of different preclinical cancer models representing diverse tumor types and oncogenic mutations. Antitumor effects were demonstrated in 12 subcutaneous xenografts, one orthotopic xenograft, and one transgenic model. The majority of these experiments were performed with single oral doses of ONC201. These experiments support the conclusion that ONC201 is an effective antitumor agent in multiple preclinical cancer models with infrequent dosing. The activity of oral ONC201 was evaluated in the Eu-myc transgenic model that spontaneously develops myc-driven lymphomas at approximately Week 9 of age. Weekly oral administration of ONC201 from Weeks 9-12 of age prolonged the median survival of the mice by 4 weeks. No mice died during the course of treatment or displayed signs of toxicity.

1.7.4 COMBINATION THERAPY

A screen was conducted that combined ONC201 with FDA-approved small molecules (NCI DTP Approved Set IV) used in oncology in a panel of cancer cell lines representing a diverse array of solid tumors (brain, breast, colon, liver, lung, ovarian). Several approved oncology drugs of diverse drug classes synergized with ONC201 under particular conditions in the screen. Notable exceptions were the lack of synergy observed with any mTOR or EGFR/MAPK signaling inhibitors. This observation is in accordance with the previous report on ONC201 (Allen et al., 2013) that demonstrates the inhibition of Akt and MAPK signaling following ONC201 monoagent treatment. Lack of synergy with anti-angiogenic agents were also noted, which is expected, as angiogenesis is not represented in standard cell culture models.

Nine approved oncology drugs were identified for validation based on the amount of synergy and the number of instances of synergy observed in the screen: azacitidine (cytidine analogue); bortezomib (proteasome inhibitor); dacarbazine (alkylating agent); hydroxyurea (nucleotide metabolism inhibitor); pralatrexate (antifolate); romidepsin (HDAC inhibitor); sorafenib (multi-kinase inhibitor); topotecan (anti-microtubule); and vismodegib (SMO inhibitor). We evaluated the combinatorial activity of these agents with ONC201 in multi-dose cell viability assays in the cell lines where synergy was previously demonstrated. The combination of ONC201 with these agents generally results in a complete elimination of tumor cells at the higher tested doses. The validation results were prioritized as a function of synergistic activity as well as efficacy. Six of the nine validated agents met the prioritization criteria of imparting >20% increased reduction in cell viability over the expected observations and a >25% reduction in absolute cell viability with the combination: azacitidine; bortezomib; dacarbazine; hydroxyurea; sorafenib; and vismodegib. Sorafenib possessed

the highest number of data points in the validation data set that met our prioritization criteria, demonstrating synergy in HCT116 and A172 cell lines at multiple doses.

The combination of ONC201 and sorafenib had a cooperative effective on induction on TRAIL and DR5 in HepG2 human hepatocellular carcinoma cells. Sorafenib also may synergize with ONC201 due to its impact on several regulators of apoptosis. Among IAP and Bcl-2 family members,

sorafenib downregulates expression of survivin and XIAP in HepG2 cells. Sorafenib also negatively regulated Mcl-1, Bax, Bak, cIAP1, and survivin in HCT116 cells that undergo apoptosis in response to ONC201 treatment. In vivo, ONC201 and sorafenib cooperated to yield complete tumor regressions in HepG2 subcutaneous xenografts.

1.8 NONCLINICAL TOXICOLOGY

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 rats, 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.

1.8.1 NON-GLP TOXICOLOGY STUDIES IN RATS

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

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

ONC201 by intravenous infusion over 30 minutes resulted in the death of one male rat. Administration of 200 mg/kg ONC201 by a 2-hour infusion resulted in the death of both animals during the infusion period. Following these observations, the tolerance of oral ONC201 was explored given the potential to lower acute toxicity by lowering Cmax. Clinical observations with oral exaggerated doses of ONC201 included decreased activity, abnormal gait and stance, prostration, irregular respiration, moderate twitching, red discharge on the muzzle, scant feces, hunched

posture, not eating, pilerection, and skin cold to touch. The NOAEL following administration of ONC201 to Sprague-Dawley rats by oral gavage was 225 mg/kg.

1.8.2 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.

1.9 GLP TOXICOLOGY AND SAFETY STUDIES

1.9.1 SINGLE DOSE ORAL TOXICITY STUDY IN DOGS (GLP)

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

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

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

1.9.2 SINGLE DOSE ORAL TOXICITY STUDY IN RATS (GLP)

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, or 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.

1.10 PHARMACOKINETICS

1.10.1 PHARMACOKINETICS IN ANIMALS

The measured half-life of ONC201 in mice is ~6 hours with intravenous administration as measured by an HPLC-UV assay. In rats, exposure to ONC201 was dose-dependent and approximately dose-proportional. Exposure to ONC201 was slightly greater in female rats after a single oral gavage dose. Plasma T1/2,e ranged from 2.3 to 8.4 hours in 7 of 8 profiles. Clearance ranged from 7.5 to 23.5 L/hr/kg in 7 of 8 profiles. Volume of distribution ranged from ~49 to ~103 L/kg in 6 of 8 profiles.

In dogs, exposure to ONC201 following oral gavage dosing at 4.2, 42, and 120 mg/kg ONC201 was dose-dependent and increased with greater ONC201 dose levels. Exposure to ONC201 was similar in male and female dogs with the observation that all mean male Cmax and AUC values were slightly greater than those corresponding female values. Elimination of ONC201 from plasma was similar between the mid and high dose levels; mean T1/2,e ranged from 4.6 to 7.8 hours. Mean T1/2,e following the low dose of 4.2 mg/kg was ~1 hour [the half-life determined for dogs in the low dose group may represent more of a distribution phase half-life rather than the terminal plasma elimination half-life]. Overall elimination of ONC201 was greater following the low dose.

1.10.2 PHARMACOKINETICS 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 1.10). 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 (Supplemental Figure 2G-H). 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 (Supplemental Figure 2K), showing a similar trend to un-normalized CL/F.

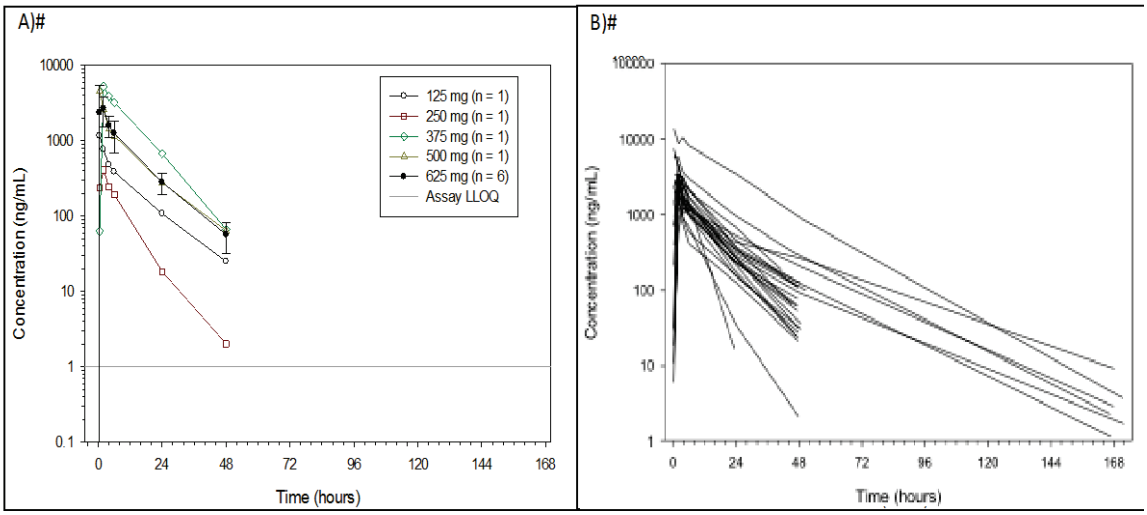


Figure 1.10: Mean ONC201 plasma concentrations versus time following the first dose of ONC201. Concentrations are shown as (A) A mean for each dose cohort, or (B) for individuals treated at 625 mg. Error bars indicate standard deviation.

Table 1.1 ONC201 pharmacokinetic parameters determined in patients receiving 625 mg ONC201 (n=24).

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

1.11 RESPIRATORY STUDIES

A GLP study was performed to determine the potential effects of ONC201 dihydrochloride on

respiratory function in rats following a single oral gavage administration. 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 that was recovering within 1 hour of administration and recovered within 2 hours of administration.

1.12 CARDIOVASCULAR

A cardiovascular study was conducted as a component of the GLP safety dog study that included controls and cohorts receiving a single oral dose of ONC201 (4.2, 42, 120 mg/kg). ECGs were obtained from all animals prior to treatment initiation and on Day 1 between 2 and 4 hours post-dose. Blood pressure was obtained from all animals prior to treatment initiation and on Day 1 between 2 and 4 hours post-dose. There were no ONC201 effects on ECG rhythm or morphology in dogs in this study nor were there any definitive ONC201-related effects on mean heart rate or arterial blood pressure noted at 1 to 2 hours post-dose.

1.13 CENTRAL NERVOUS SYSTEM

1.13.1 RATS

Functional Observational Battery was observed prior to treatment initiation and on Day 1 between 1 and 2 hours post-dose. For clinical observations, there were no clinical signs of toxicity noted at single doses up to 125 mg/kg ONC201. At a dose of 225 mg/kg, clinical signs of toxicity were limited on the day of dose administration to one male and one female 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.

1.13.2 DOGS

Functional Observational Battery was observed prior to treatment initiation and on Day 1 between 1 and 2 hours post-dose. Findings for the functional observational battery performed between 1 and 2 hours post-dose on Day 1 were limited to the same noted by the clinical observations. Clinical observation for the 42 mg/kg dose group, changes in fecal excretion were noted in 3/6 males and 1/6 females, increases in secretion (salivation) were noted in 1/6 males and vomitus was noted in 3/6 males and 1/6 females. For the 120 mg/kg dose group, changes in fecal excretion were noted in 4/6 males and 3/6 females, increases in secretion (salivation) were noted in 5/6 males and 1/6 females and vomitus was noted in 3/6 males and 4/6 females.

1.14 NONCLINICAL PHARMACOKINETICS, METABOLISM, AND DOSE SELECTION

The absorption, distribution, metabolism, and excretion of ONC201 in humans are unknown. The pharmacokinetics of ONC201 has been studied in mice, rats, and dogs. The Tmax was at 1 hour (which was first sampling point) and the terminal half-life was 4.6 to 8.4 hours. The drug was dose proportional in rat. In the dog the drug was dose proportional at the two highest doses studied.

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.

The total exposure to ONC201 does not appear to correlate with efficacy in nonclinical studies. Single dose ONC201 delivered by oral administration or intraperitoneal injection caused similar tumor stasis in a subcutaneous tumor xenograft in athymic nude mice. A single oral dose of 25 mg/kg ONC201 yielded peak efficacy in another subcutaneous xenograft model, with higher doses yielding similar efficacy. Furthermore, the antitumor activity was equivalent in the long term between cohort receiving the optimal dose of 25 mg/kg ONC201 once a week, twice a week, and once every two weeks. This observation is in accordance with delayed and sustained activity of ONC201 observed in vitro or in vivo.

The acute toxicity of ONC201 appears to be related to Cmax. Thus acute toxicities are readily alleviated with oral administration or with extension of infusion time, which lowers the Cmax. Interestingly, the acute toxicities observed with ONC201 are generally mild, transient, and occur within a few hours of administration, unlike the antitumor mechanism of ONC201. These observations strongly suggests that the acute toxicity associated with ONC201 is an off-target effect that occurs at higher than necessary doses, rather than being directly associated with the mechanism that confers efficacy.

The short half-life of the molecule suggests that drug-drug interactions are unlikely and that combining ONC201 with radiation or other therapies may be well tolerated and effective, based on the prolonged biological activity of ONC201. Given the rapid systemic clearance of ONC201, drug accumulation with ONC201 at the infrequent dosing schedule is unlikely, providing another safety feature for the drug.

In GLP safety studies in rats and dogs with ONC201, there were no deaths or dose limiting toxicities. In general, adverse events associated with exaggerated doses of ONC201 were mild and reversible. The only findings that were observed in both rats and dogs were decreased activity, decreased food consumption (weight loss only seen in rats), and salivation. Given the safety profile of this drug and the intended indication of advance cancer patients, the benefit-risk profile is favorable and the Sponsor believes that ONC201 warrants clinical evaluation.

The starting dose for the first-in-man trial was calculated following the ICH S9 Guidance Document. The NOAEL and calculations are given below. The start dose was selected as 125 mg based on rounding the lowest dose, which was based on the rat NOAEL.

		Species dose (mg/kg)	Human equivalent dose (mg)*	Ratio to Expected Therapeutic Dose
Rats	Cohort 1	0	0	N/A
	Cohort 2	12.5	125	1
	Cohort 3	125	1250	10
	Cohort 4	225	2250	18
Dogs	Cohort 1	0	0	N/A
	Cohort 2	4.2	125	1
	Cohort 3	42	1250	10
	Cohort 4	120	3571	28.6

*Allometrically scaled to a human fixed dose

Calculation of Starting Dose

The starting dose in the Phase I trial was selected as 125 mg based on allometric scaling and rounding the lowest NOAEL from the GLP toxicology studies, as tabulated below. Allometric scaling was used in these calculations, which held true when scaling between rats and dogs in GLP toxicology studies. This dose was calculated as 1/10th of the rat NOAEL (rat 125 mg/kg and dog 42 mg/kg translates into a starting dose of 123 mg or 138 mg for a patient with a body weight of 60 kg).

1.15 CLINICAL STUDIES

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

An accelerated dose escalation design was employed to reduce the number of patients treated at potentially sub-therapeutic dose and to accelerate the determination of the recommended phase II dose. Ten evaluable 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 one patient per cohort until any patient experiences a grade 2 adverse event during the first cycle of treatment, defined as 21 days. Five dose levels (125 mg, 250 mg, 375 mg, 500 mg, 625 mg) were selected for the study. Enrollment at each subsequent dose level required that all patients enrolled at the prior dose level completed Cycle 1 dosing and were evaluated 21 days later to assess safety.

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

reported events that were not attributed to the study drug.

Clinical and laboratory results indicated that the drug possessed biological 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 metastases 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 every three week dosing 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 to the sponsor of any drug-related adverse events in any of these patients. All three 375mg and six of the 625mg patients have successfully completed the DLT window (21 days). Based on these findings, the recommended administration schedule of ONC201 is 625mg once every week.

Additional clinical studies of ONC201 that are active include 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), and a Phase II clinical trial in bevacizumab-naïve glioblastoma multiforme (GBM).

A clinical trial is currently being conducted at the MD Anderson Cancer Center investigating the safety of ONC201 in patients with acute leukemias and myelodysplastic syndrome (study #2014-0731;

NCT02392572). As of February 27, 2016, 3 patients have been enrolled in this study that dosed one patient at 125mg once every three weeks, the other patient at 250mg once every three weeks and a third patient at 375mg once every three weeks. There were 3 reported instances of febrile neutropenia, lung infection (pneumonia) and gastrointestinal disorders. None of these were attributed as drug-related by the Investigator.

Study #PH-077 (NCT02609230) is a Phase I dose-escalation study of ONC201 in patients with solid tumors and multiple myeloma, being conducted at Fox Chase Cancer Center. As of February 27, 2016, 5 patients have received ONC201 125mg once every 3 weeks. Patient 1 experienced an SAE that was initially assessed as possibly drug related (progressed from Grade 2 fatigue at baseline to Grade 3 fatigue). The patient had brain metastases at baseline and rapid progression of underlying disease and associated symptoms within 2 weeks of initiating ONC201 treatment. The SAE attribution that triggered the initial report is under reassessment based on the evidence of progressive underlying disease.

1.16 EFFECTS IN HUMANS

So far no serious side effects have been reported in patients with advanced solid tumors and hematological malignancies that are attributable to ONC201. Grade I adverse events that have been observed and reported include fever, nausea, vomiting, fatigue, and elevated serum amylase that were attributed as possibly-related to ONC201. One Grade II allergic reaction occurred that was managed with standard medications. The table below includes adverse events attributed as at least possibly-related to ONC201 in the Phase I trial in advanced solid tumors were Grade 1 (among 28 patients).

ONC201 (mg)	125	250	375	500	625
No of Patients	1	1	1	1	24
Pyrexia	1 (3.6%)	0	0	0	0
Fatigue	1 (3.6%)	0	0	0	0
Elevated amylase	0	0	0	0	2 (7.2%)
Emesis	0	0	0	0	1 (3.6%)
Nausea	0	0	0	0	1 (3.6%)

Side effects seen in animals included the following:

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

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

childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. An assessment should be made to ensure the potential benefit would justify a potential risk to the fetus.

It is not known whether ONC201 is excreted in breast milk. It is recommended that women do not breastfeed during treatment with ONC201 and for 2 months after the last dose.

All adverse events occurring with any patient participating in any clinical trials with ONC201 must be reported to the Sponsor, the IRB and to health authorities (e.g., FDA) as applicable. Refer to the study protocol for definitions of AE/SAE, assessment criteria and reporting responsibilities.

1.17 STUDY 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. Malignant B cells are highly sensitive to ER stress-inducing agents that trigger the ISR such as proteasome inhibitors. 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 B cell malignancies such as mantle cell lymphoma. 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. B cell malignancies 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.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE OF PHASE 1

- To determine recommended Phase 2 dose for oral ONC201 in patients with relapsed/refractory lymphomas.
- To identify toxicities associated with oral ONC201 in patients with relapsed/refractory lymphomas.

2.2 SECONDARY OBJECTIVE OF PHASE 1

- To determine the pharmacokinetics (PK) of oral ONC201 following administration.
- To observe the anti-tumor effects of oral ONC201, if any occur, in patients with relapsed/refractory lymphomas.
- To correlate blood and tumor markers in CTCL patients (protocol PA18-0191).

2.3 PRIMARY OBJECTIVES OF PHASE 2

- To determine the objective response rate to ONC201 in patients with relapsed/refractory lymphomas.

2.4 SECONDARY OBJECTIVES OF PHASE 2

- Confirm tolerability of recommended Phase 2 dose.
- Assess clinical outcomes associated with ONC201 treatment in patients with relapsed/refractory lymphomas.
- Correlate clinical outcome with tumor and serum biomarkers.
- Correlate blood and tumor markers in CTCL patients (Protocol PA18-0191)

3 ENTRY CRITERIA

3.1 INCLUSION CRITERIA

1. Phase 1 and Phase 2: Confirmed diagnosis of previously treated relapsed and/or refractory lymphoma. Patients with CNS lymphoma are included.
2. Age ≥ 18 years at the time of signing the informed consent.
3. Patient with leukemia phase (peripheral blood involvement), CNS lymphoma (including CSF-only disease), non-measurable disease, gastrointestinal (GI) MCL, or bone marrow (BM) MCL are also eligible. Gastrointestinal or bone marrow or spleen only patients are allowable and will be analyzed separately.
4. All adverse events related to prior therapies (chemotherapy, radiotherapy, and/or surgery) must be resolved to ≤ Grade 1, except for alopecia.
5. Patients must be willing to receive transfusions of blood products.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (see Appendix 3).
7. Patients must have the following clinical laboratory values:
    - Serum creatinine < 2.0 mg/dl.
    - Serum bilirubin < 1.5 mg/dl
    - Platelet count > 50,000/mm^3
    - Absolute neutrophil count (ANC) > 1,000/mm^3
    - Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) < 2 x upper limit of normal or < 5 x upper limit of normal if hepatic metastases are present.
8. Willing and able to participate in all study related procedures and therapy including swallowing capsules without difficulty.
9. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test and must be willing to use acceptable methods of birth control during the study and for 90 days after the last dose of study treatment. Acceptable methods of birth control include condoms with birth control foam, birth control pills, implantable or injectable birth control, birth control patch, intrauterine device (IUD), or diaphragm with spermicidal gel. Male patients must use an effective barrier method of contraception (i.e., condoms with birth control foam or diaphragm with spermicidal gel) during the study and for 90 days following the last dose of study treatment if sexually active with a female of childbearing potential. Contraception must be in place at least 2 weeks prior to initiating study treatment.
10. Patient must be English-speaking (MDASI completion only)

† A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

3.2 EXCLUSION CRITERIA

1. Any serious medical condition including but not limited to, uncontrolled hypertension, uncontrolled diabetes mellitus, uncontrolled infection, active/symptomatic coronary artery disease, COPD, renal failure, active hemorrhage, or psychiatric illness that, in the investigators opinion places the patient at unacceptable risk or would prevent the subject from signing the informed consent form.

2. Pregnant or breast feeding females.
3. Use of any standard/experimental anti-lymphoma drug therapy, including steroids (dexamethasone dose ≥ 4 mg/day or prednisone ≥ 20 mg/day), within 3 weeks of initiation of the study or use of any experimental non-drug therapy (e.g., donor leukocyte/mononuclear cell infusions) within 56 days of initiation of the study drug treatment. Hydroxyurea is permitted up to 24 hours before the first dose of study drug in patients with rapidly- proliferating disease.
4. Prior allogeneic stem cell transplant (SCT) within 16 weeks or autologous SCT within 8 weeks of initiation of therapy. Patients that require immunosuppressive therapy are not eligible within 60 days of therapy.
5. History of HIV infection. Patients with active Hepatitis B infection (not including patients with prior Hepatitis B vaccination; or positive serum Hepatitis B antibody). Hepatitis C infection is allowed as long as there is no active disease and is cleared by GI consultation. HIV screening is not required for this study.
6. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to enrollment.
7. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or any other gastrointestinal condition that could interfere with the absorption and metabolism of ONC201
8. Major surgery within 4 weeks of initiation of therapy.
9. The patient has a prior or concurrent malignancy that in the opinion of the investigator, presents a greater risk to the patient's health and survival, than of the MCL, within the subsequent 6 months at the time of consent. Investigator discretion is allowed.
10. Patients with NYHA Class III and IV heart failure, myocardial infarction in the preceding 6 months, and significant conduction abnormalities, including but not limited to 2nd degree AV block type II, 3rd degree block, QT prolongation (QTc > 500 msec), sick sinus syndrome, ventricular tachycardia, symptomatic bradycardia (heart rate < 50 bpm), hypotension, light headedness and syncope. Patients with active atrial fibrillation will be excluded. The protocol excludes patients who have within the past year had a stent and by recommendation of their cardiologist need to stay on anticoagulants such as warfarin equivalent vitamin K antagonist.
11. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ONC201 or its excipients.
12. Acute infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to initiation of study.
    Active alcoholism or use of recreational drug (evaluated by history taking).

4 STUDY DESIGN AND TREATMENT SCHEDULE

4.1 STUDY DESIGN

This will be a single-center, Phase 1/2 clinical trial in patients with refractory or relapsed lymphoma. The feasibility of administrating ONC201 and the recommended Phase 2 dose (RP2D) will be determined in Phase 1. The tolerability and objective response rate at the RP2D will be evaluated in Phase 2.

4.1.1 PHASE 1

In the Phase I portion of the study, up to 5 pre-specified dose levels will be examined using the standard modified Fibonacci 3 + 3 design. ONC201 will be dosed orally once every 3 weeks (Arm

A) or once every 1 week (Arm B).

Subsequent to the February 9, 2016 amendment is IRB approved, enrollment in Arm A will cease. Patients already enrolled in Arm A continue to receive ONC201 on the same dose regimen, as stipulated by the protocol (see Section 6.6).

No intrapatient dose escalation or cross-over to Arm B is permitted. Dose escalation will continue until an MTD is reached or dose level 5 is reached (625 mg), which will be declared the maximum administered dose (MAD). The MAD or MTD, whichever is reached first in Arm B, will be defined as the recommended Phase 2 dose (RP2D). It is anticipated that the eligible number of patients required for this Phase 1 part will be 36 patients.

A Phase I study has established 625mg ONC201 every one week as the recommended Phase II dose that is very well tolerated (see Section 1.15). Subsequent to IRB approval of the September 9, 2016 amendment, enrollment in Phase I will cease and all new patients will be enrolled in Phase II.

4.1.2 PHASE 2

Once the RP2D is determined, an expansion of 30 additional patients will be treated at the RP2D. The primary endpoint is response rate, CR + PR. (For cutaneous T cell lymphomas, please refer to appendix 5 to 12 for disease classification and response assessments. Please also note that a separate correlative study (PA18-0191) will be conducted in parallel. PA18-0191 is approved by the MD Anderson IRB and will be co-submitted with protocol 2014-0630.)

4.2 TREATMENT SCHEDULE

All patients shall be registered with CORe (Clinical Oncology Research System) at (713) 745-2673 prior to receiving therapy.

ONC201 will be administered in the clinic, i.e. as direct-observed therapy, for days when PK/PD samples are collected. Self-administration is permitted for days when the patient is not coming into the clinic for any other reason.

All patients will be asked to record the medications they take at home and to bring the medication record they use to the clinic with them when they return to see their physician or research nurse. The patients will be provided with a specific medication form on which to record this information. Patients will also be asked to report any adverse events they experience during the course of the study. They will be given a form on which to record their information and this form will be returned on their next clinic visit to assist the research personnel in determining adverse events.

The dose of ONC201 will be assigned as described below. Following Cycle 1, therapy will continue in 21-day cycles, until there is disease progression, unacceptable toxicity or the patient chooses to

withdraw from therapy. Growth factors and transfusions as needed are allowed after Cycle 1.

Overall response rate (ORR) (complete response + partial response [PR]) will be assessed by the Revised International Workshop Standardization Response Criteria for Non-Hodgkins Lymphoma (Appendix 2), with secondary assessment of the duration of response (DOR), progression free survival (PFS) and overall survival (OS). (For cutaneous T cell lymphomas, please refer to appendix 5 to 12 for disease classification and response assessments.)

4.3 ONC201 STUDY DRUG ADMINISTRATION

ONC201 capsules are intended to be administered orally. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Patients should take designated capsules of ONC201 at approximately the same time of day for each administration and food should not be consumed either 2 hours prior or 2 hours post administration. ONC201 should be taken with a glass of water and consumed over as short a time as possible.

If a dose is missed, it can be taken up to 6 hours after the time it would have been taken. If it is later than 6 hours, subjects should skip the dose.

If a dose is vomited and the subject can see all of the capsules taken, they can retake the dose. If a dose is vomited and the subject cannot see all of the capsules, they should not retake the dose. The dose should be taken at the same time as usual the next day.

4.4 DOSE LEVELS TO BE STUDIED

ONC201 will be administered every 21 days in Arm A or every 7 days in Arm B. The same dose levels will be studied in Arm A and Arm B. The first cohort of subjects in each arm will receive Dose Level 1.

Dose Level	Dose of ONC201 (mg)
Level 1	125
Level 2	250
Level 3	375
Level 4	500
Level 5	625

4.5 DOSE ESCALATION PROCESS

The first cohort of three subjects enrolled into the study will receive Dose Level 1. Following the enrollment of the first patient in each cohort, the patient will be observed for 7 days prior to the second and third patient being enrolled into that cohort. A full safety evaluation will be conducted

when these subjects have completed one cycle (21 days) of therapy. Prior to advancing/changing dose levels a cohort summary must be completed and submitted to the IND Medical Monitor for review and approval. All subjects enrolled into each cohort must complete one cycle of treatment prior to enrolling subjects into higher dose levels. Dose escalation for subsequent patients will proceed as follows:

- If no Dose Limiting Toxicity (DLT) is reported in the first three subjects at a dose level, that dose level will be considered safe and three subjects will be enrolled at the next dose level. Toxicity information will continue to be evaluated from the time of the first protocol-specific intervention, until 30 days from the last dose of study drug.
- If 1/3 subjects in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable subjects.
- If 2/3 subjects in a cohort at a dose level has a DLT, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*.
- If there are < 2 subjects with a DLT among the expanded cohort of six evaluable subjects a cohort of three subjects will be enrolled in the next higher dose level.

If there are 2 or more subjects with a DLT among the expanded cohort of six evaluable subjects, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded*. The previous dose level at which $\leq$ 1 of 6 patients experienced DLT will be declared the MTD.

When the MTD has been exceeded:

If less than 6 subjects have been treated in the next lower dose level (the possible MTD level), additional subjects will be entered into this dose level until there are 6 subjects treated. If $\leq$ 1 of these 6 subjects encountered DLT, then this dose level will be declared to be the MTD. If 2 or more of the 6 subjects encounter DLT, then the MTD has been exceeded.

4.6 SUBJECT REPLACEMENT

Subjects, who discontinue study drug prior to the completion of their first 21-day study assessments for a reason other than an adverse event, will be replaced in order to have an adequate number of subjects for determination of the MTD.

4.7 DETERMINATION OF MAXIMUM TOLERATED DOSE

4.7.1 MAXIMUM TOLERATED DOSE

The maximum tolerated dose is defined as the highest dose that causes dose limiting toxicity in less than one third of patients treated out of a 6 patient cohort, during the first cycle of treatment.

Patients Experiencing DLT	Required Action

0/3	Escalate to next dose level
1/3	Add 3 patients at current dose level
1/6	Escalate to next dose level
2/2, 2/3, 2/4, 2/5, 2/6	MTD exceeded – Confirm with previous dose level with a total of 6 patients

NOTE: No more than 6 evaluable patients may be enrolled per dose level.

4.7.2 DOSE LIMITING TOXICITY

Dose limiting toxicity (DLT) will be assessed during the first course of each cohort (21 days), and refers to a study drug related or possibly related event which meets one of the following criteria using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03:

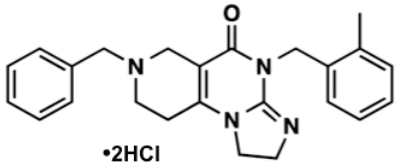
- Grade 3 or higher non-hematologic toxicity.
- Grade 4 hematologic toxicity (ANC < 0.5 X 10^9/L and Platelet count < 25 X 10^9/L both figures are considered DLT). [If bone marrow infiltration Platelet count < 15 X 10^9/L for the purposes of determining DLT)] Any grade 4 hematologic toxicity is a DLT, including anemia.
- Grade 3 neutropenia with elevated fever (defined as ANC < 1.0 X 10^9/L and > 101 degrees F to be confirmed on two occasions).

  Inability to receive the scheduled Day 1 dose of Cycle 2 within 14 days due to drug related toxicity persisting from Cycle 1 or drug related toxicity newly encountered on Day 1 of Cycle 2.

5 ONC201 STUDY DRUG SUPPLY

5.1 DESCRIPTION

The study drug ONC201 is provided as 125 mg free base (approximately 150 mg of dihydrochloride), without any excipients, filled into hydroxypropyl methylcellulose (HPMC) capsule shells. ONC201 investigational drug product is intended for oral administration. Below is the chemical name and structural depiction of ONC201•2HCl.

Chemical Name(s)	• 7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one•2HCl
Molecular Structure	

Molecular Formula	$C_{24}H_{26}N_4O$ (free base) $C_{24}H_{26}N_4O$•2HCl (salt)
Molecular Weight	386.49 (free base) 459.41 (salt)

5.2 FORMULATION

Each capsule of drug product contains the equivalent 125mg of anhydrous ONC201 free base with or without microcrystalline cellulose. This corresponds to ~150mg of drug substance that corrects for the ONC201 dihydrochloride salt and moisture.

5.3 SHIPPING AND STORAGE

Study drug will be shipped to M.D. Anderson Cancer Center Investigational Pharmacy before subjects are enrolled in the study.

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).

5.4 DRUG ACCOUNTABILITY

MD Anderson Cancer Center's Investigational Pharmacy will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of capsules contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the capsules, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Oncoceutics, Inc. and by regulatory authorities.

Empty and partially used containers should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Oncoceutics, Inc. and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Investigators are prohibited from supplying ONC201 capsules to any subjects not properly enrolled in this study or to any physicians except those designated as sub-investigators on Form FDA1572. The investigator must ensure that subjects receive ONC201 capsules only from personnel who fully understand the procedures for administering the drug.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form or similar should be completed and sent via email to Oncoceutics Drug Safety or designee by MD Anderson Cancer Center's Investigational Pharmacy. Refer to the IB for additional information regarding the drug product to be used in this trial.

6 DOSE MODIFICATIONS AND INITIATION OF A NEW CYCLE OF THERAPY

Subjects will be evaluated for AEs at each visit with the NCI Common Toxicity Criteria, Version 4.3 (see Appendix 4) used as a guide for the grading of severity. Refer to Section 6.1 for dose reduction steps and Section 6.2 for instructions on dose modifications.

No dose modifications are permitted during Cycle 1 unless a DLT has been experienced. No dose escalations are permitted in any given patient once a dose level has been assigned. Patients experiencing DLT during Cycle 1 may continue on therapy if the toxicity can be managed according to the dose modification guidelines outlined below. However, the DLT event will contribute to the assessment of MTD for that given cohort.

Dose modifications may be performed for all subsequent cycles. If the toxicities cannot be managed by dose modification, the subject has to be withdrawn from the trial. Subjects who cannot tolerate ONC201 should be discontinued from the study (unless the subject has achieved a plateau phase of response to study therapy; such subjects will continue to adhere to the schedule of assessments followed during the treatment phase of the study even though study drug has been discontinued). Subjects who receive a dose of 80 mg and require a dose reduction should be discontinued from the study.

6.1 ONC201 DOSE REDUCTION STEPS

ONC201 Dose Reduction Steps		
Starting Dose	**Step –1**	**Step –2**
125 mg	NA	NA
250 mg	125 mg	80 mg
375 mg	250 mg	125 mg
500 mg	375 mg	250 mg
625 mg	500 mg	375 mg

6.2 DOSE MODIFICATION GUIDELINES

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**	**Dose Modification Guidelines** **at any time DURING A CYCLE of therapy**
HEMATOLOGICAL TOXICITIES	

Thrombocytopenia	Grade 4 (< 25 x 10^9/L) or Grade 3 or 4 with bleeding.	Temporarily discontinue ONC201. Repeat CBC weekly. If not resolved to ≤ grade 1 within the cycle, start new cycle with one level dose reduction of ONC201 when the criteria for a new cycle are met. (Transfusion support is permitted following cycle 1unless the patient experiences a DLT)
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L) (**This is considered a DLT**)	Temporarily discontinue ONC201 Repeat CBC weekly. If not resolved to ≤ grade 1 within the cycle, start new cycle with one level dose reduction of ONC201when the criteria for a new cycle are met.
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue ONC201. Repeat CBC weekly. If not resolved within the cycle, start new cycle with one level dose reduction of ONC201 when the criteria for a new cycle are met.
NON-HEMATOLOGICAL TOXICITIES		
Tumor Lysis Syndrome	(≥ 3 of the following: ≥ 50% increase in Cr, uric acid, or	Hold ONC201 until all serum abnormalities have resolved. Take
	phosphate ≥ 30% increase in K; ≥ 20% increase in calcium; or ≥ 2 fold increase in LDH)	precautionary measures and resume at full dose or one level reduction at the investigators discretion.
Herpes Zoster	Any Grade	Hold ONC201 until lesions are dry. Restart at full dose.

Peripheral Neuropathy	Grade 2 with pain or ≥ grade 3	If persists for more than 2 week hold ONC201 until resolved to ≤ grade 1 without pain. Restart at one level dose reduction.
	Grade 4	Discontinue ONC201
Congestive Heart Failure	Any grade	Hold ONC201 until resolution or return to baseline. Continue at one level dose reduction. If not resolved within 14 days discontinue ONC201
Infection	Grade 3 or 4	Hold therapy until systemic treatment is complete. May resume at same dose level.
Renal Insufficiency	CrCl ≤ 30 mL/min	Hold ONC201 until resolved and resume at one level dose reduction.
Any other drug related toxicity	≥ Grade 3	Hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction
All dose modifications should be based on the worst preceding toxicity.		
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)		
*** See also concomitant medication Section 6.4		

6.3 INITIATION OF A NEW CYCLE OF THERAPY

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is > 750/µL (growth factors allowed)
- Platelet count > 50,000 (transfusions allowed)
- (Patients who have bone marrow infiltration by MCL, DLBL, and/or TLCL are eligible if their ANC is ≥ 500/mm3 [growth factor allowed] or their platelet level is equal to or > than 30,000/mm3. These patients should be discussed with either the PI or Co-PI of the study before treatment begins).
- Hgb > 8 g/dL (red cell transfusions support is permitted)
- Any other drug related adverse event that may have occurred has resolved to < Grade 1 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly. A new cycle will not be initiated until the toxicity has resolved as described above. In the event that a new cycle cannot be initiated within 3 weeks of a scheduled Day 1, the patient must be removed from study, unless in the opinion of the investigator the patient was benefitting from therapy. In this case, continuation of therapy must be approved by the Investigator.

6.4 CONCOMITANT THERAPY

All medications (prescription and non-prescription), treatments and therapies taken from the first day

of study drug through the end of the study, must be recorded on the source documents and PDMS. Concomitant use of other anti-lymphoma therapy, including steroids, while the subject is on study drug is prohibited. Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose ≥ 4 mg/day or prednisone ≥ 20 mg/day are not permitted.

The use of filgrastim (G-CSF) and erythropoietin for subjects in this study is permitted when used to treat neutropenia and anemia, respectively. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics and prophylactic treatment for potential hypersensitivity reactions and tumor lysis syndrome when appropriate.

Avoid co-administration of acid-reducing agents as these agents may decrease the systemic exposure of ONC201. If acid-reducing agents cannot be avoided, use antacids instead of proton pump inhibitors or histamine-2 receptor antagonists.

6.4.1 REQUIRED PREGNANCY PREVENTION

Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test prior to initiation of therapy and must use acceptable methods of birth control during the study and for 90 days after the last dose of study drug. Men must agree to use a latex condom during sexual contact with a female of childbearing potential during the study and for 90 days after the last dose of study drug even if they have has a successful vasectomy.

6.4.2 SAFETY CONSIDERATIONS

The safety profile of ONC201 in humans is unknown. Adverse reactions may occur following treatment with ONC201. All subjects participating in trials of ONC201 should be closely monitored for the occurrence of adverse events.

Because the potential for interaction of ONC201 with other concomitantly administered drugs through the cytochrome P450 system is not known, the patient should avoid taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with ONC201 until the infection has resolved and if being treated with anti-infective, the course of antibiotics has been completed.

Hydroxyurea used to control peripheral blast counts is permitted within the first 2 cycles of treatment on study, but it must be stopped at least 24 hours before study drug administration in Cycle 3. Hydroxyurea also is permitted up to 24 hours before the first dose of study drug in patients with rapidly-proliferating disease.

6.5 TREATMENT COMPLIANCE

Treatment will be administered on an outpatient basis and each dose of administration will be documented in the drug accountability records and source documentation.

6.6 DISCONTINUATION FROM TREATMENT

Treatment with study drug is to be discontinued when any of the following occur:

- Disease Progression: Patients will be taken off-study if they have progressive disease (PD) or clinically significant deterioration at any time during the study.
- Personal Reasons: Patients may choose to withdraw from the study at any time.
- Adverse Event(s) (AEs) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Clinical Judgment of the Investigator: A patient may be withdrawn from the study, if in the opinion of the investigator, it is not in the patient's best interest to continue.
- Requiring other anti-neoplastic therapies.
- Major violation of the study protocol (i.e., unable to adhere to study schedule).
- Lost to follow-up.
- Death.
- Confirmed or suspected pregnancy.

The date of discontinuation and reason(s) for patient discontinuation from the study will be recorded in the chart and CORe. All evaluations which are required at the final study visit will be conducted within 30 days of the last study drug treatment for each patient who discontinues treatment (with the exception of patients that withdraw consent). Subjects will be followed for toxicity for 30 days after the last dose of study drug(s).

7 VISIT SCHEDULE AND ASSESSMENT

7.1 STUDY PROCEDURES

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. Screening assessments occur within 28 days from first day of study drug administration (Cycle 1, Day 1). All laboratory assessments are to be done with 14 days of first day of study drug administration, unless otherwise noted.

End of study evaluation should be scheduled within 30 days of the last study treatment or within 30 days of study discontinuation (with the exception of discontinuation due to patient withdraw of consent). Follow-up contact with subjects should occur at a minimum of every 3 months via telephone from end of study date for a maximum of one year. An unscheduled visit can occur at any time during the study. Source documentation must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded in PDMS. PDMS/CORe will be used as the electronic case report form for this study. Source documents for these unscheduled visits must also be maintained.

A schedule of the assessments can be found in Appendix 1, Schedule of Study Assessments.

7.1.1 SCREENING ASSESSMENTS

Screening visits may be scheduled within 28 days. See Appendix 1 for a list of required screening assessments. For cutaneous T cell lymphomas, please refer to Appendix 13.

7.1.2 ON-STUDY AND END OF STUDY ASSESSMENTS

Study visits and procedures may be scheduled with a +/- 3 day window except for Screening visit. See Appendix 1 for timing of all assessments. For cutaneous T cell lymphomas, please refer to Appendix 13.

7.1.3 EFFICACY ASSESSMENT

The endpoint for evaluating efficacy will be the objective response rate.

Response definitions for measurable disease from the Revised International Workshop Standardized Response Criteria for non-Hodgkin's Lymphoma will be used (see Appendix 2). For cutaneous T cell lymphomas, please refer to Appendix 5 to 12 for disease classification and response assessments

7.1.4 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry values, vital signs, ECOG performance status, and the regular physical examinations, ECG assessments and neurological assessments.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. CTCAE v4.03 can be accessed on the NIH/NCI website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

7.1.5 PHARMACOKINETICS

For each patient, 3 tubes of > 5 mL of blood per tube will be collected into 2 EDTA tubes and 1 tube without anticoagulation. After the first dose of Cycle 1, the time points for blood draws will be at baseline, at 30 minutes (± 15 minutes), 2 hours (± 30 minutes), 4 hours (± 30 minutes), 6 hours (± 30 minutes), 24 hours (± 1 hour), 48 hours (± 3 hours), 72 hours, 96 hours, and 168 hours (± 24 hours) (following the first dose only). Thereafter, a pre-dose blood draw for PK will be taken on day 1 of Cycles 2 and beyond and one additional blood draw will occur at the end of study visit. For the second dose of ONC201, pre-dose blood samples will be drawn as a trough of the first dose. All samples will be stored cryogenically until analysis.

7.1.6 ECG ASSESSMENTS

Single ECG assessments will be performed with standard 12-lead procedures. ECGs should be performed at the time points indicated in the Study Calendar: baseline, Cycle 1 Day 1 (15 minutes ± 10 minutes, 1 hour ± 15 minutes, and 2 hours ± 30 minutes post-dose), Cycle 1 day 2, Cycle 1 Day 8, and when patients come off study. If indicated due to any cardiac abnormalities, two additional ECGs must be performed at intervals approximately 3 minutes apart. Abnormalities in the ECG that

lead to a change in subject management (e.g., dose reduction of withheld, treatment discontinued, requirement of additional medication or monitoring) or result in clinical signs and symptoms considered clinically significant for the purposes of this study and will be deemed adverse events.

7.1.7 CORRELATIVE STUDIES

The mechanism of action of ONC201 appears to involve induction ER stress, TRAIL, and DR5, as well as inactivation of Akt and ERK, at least in some tumor cells. Thus, the following markers will be assessed in tumor samples from consenting enrolled patients with measurable disease at baseline and post-treatment, as needed: DRD2, DRD5, TGM2, KSR-1, ATF4CHOP, DR5, Tunel, NK, CD4+ T cells, H&E, TRAIL, pERK, and pAkt. These markers will be assessed in circulating lymphoma cells as available. We will look at plasma dopamine and prolactin levels at any time point where research-related plasma samples are drawn.

In aggregate, these tests would require at least 0.5mL plasma and 11 pretreatment tissue slides plus 7 post-treatment slides.

TRAIL is localized to the cell surface, but is also cleaved to form a soluble truncated version that remains bioactive. Thus TRAIL levels will be assessed in the serum of treated patients by ELISA and in tumor cells by flow cytometry. Flow cytometry will also be utilized to investigate intratumoral expression of CHOP, DR5, phospho–ERK, and phospho-Akt.

On cycle 1, PD samples will occur at baseline, 24 ± 12 hrs, 48 hours ± 12 hours, and 168 hours ± 24 hours after administration of study drug on first cycle. A pre-dose PD sample will be taken on Day 1 of Cycles 2 and beyond and one additional PD sampling will occur at the end of study visit.

Peripheral blood will be collected in 2 EDTA tubes and 1 blood collection tube without anticoagulant.

One EDTA tube will be dedicated to PK sampling of plasma that will be divided into 1mL aliquots to avoid freeze-thaw cycles during analysis. The other EDTA tube will be used for PD to harvest circulating cells by centrifugal separation with Ficoll-Paque while the other tube, from which protein and RNA .

The PD tube without anticoagulant will be allowed to clot, and serum will be harvested by iterative centrifugation for serum analysis (e.g., ELISA). All samples (protein, RNA, plasma, and serum) will be stored cryogenically until analysis.

For cutaneous T cell lymphomas, please note that a separate correlative study (PA18-0191) will be conducted in parallel. PA18-0191 is approved by the MD Anderson IRB and will be co-submitted with protocol 2014-0630. Sample collections will mirror the time points for the CTCL arm as specified in Appendix 13. Briefly, at pre-dose Cycle 1 Day 1, and pre-dose Cycle 2 Day 1, blood will be drawn into 2 mononuclear cell preparation tubes, 1 Streck tube, and 1 serum collection tube, for peripheral blood

mononuclear cells (PBMC) separation, DNA/RNA extraction, and serum collection. The protein expression of ATF4, AKT, TRAIL, JAK/STAT, and NFκB molecules in T-cells will be evaluated by flow cytometry or/and western blot. Total RNA will be extracted from PBMCs and mRNA expression of aforementioned molecules will be evaluated by mRNA arrays. Flow cytometry will be performed at baseline and every 3 cycles on patients with stage B2 or B1 at baseline to assess CD4+, CD8+ and CD4+26- or CD7- T-cells in peripheral blood. Cytokines and soluble molecules in serum/plasma will be tested by cytokine array. In addition, at pre-dose Cycle 1 Day 1, and pre-dose Cycle 2 Day 1, 6mm punch biopsy will be collected to determine subsets of CD3, CD4, CD8 T-cells in epidermis and dermis, and protein expression including aforementioned biomarkers for ONC201 activity. The mRNA expression in skin lesions will also be evaluated by mRNA arrays and confirmed by immunohistochemistry

7.1.8 MD Anderson Symptom Inventory (MDASI)

The MD Anderson Symptom Inventory (MDASI) will be used to assess symptomatic status of the patients. The MDASI is a patient-reported outcome measure of the severity at its worst and interference with daily activities in the last 24 hours of common symptoms of cancer and its treatment.1 The MDASI has several advantages over other measures2,3: it is comprehensive yet brief enough to avoid being a burden to answer, it assesses both the severity of cancer-related symptoms and the level of symptom interference with functioning, its 0 to 10 numeric scale is readily understood by patients, and adaptable for telephone and electronic administration. The numeric rating scales are anchored on the ends with the descriptors 0=symptom not present or no interference and 10=the symptom is as bad as can be imagined or complete interference.1 Patients will complete the MDASI starting at screening and weekly until the start of therapy. The MDASI will then be completed weekly beginning on the day after the first dose of study drug for the first 3 cycles of therapy. Patients will then complete the MDASI the day after the start of each cycle of therapy and approximately 30 days (+/- 3 days) after discontinuation of study drug or before the start of subsequent treatment (whichever occurs first). In follow up, patients will complete the MDASI every 3 months for 1 year. MDASI assessments may be completed on paper or electronic tablet when the patient is in clinic. When the patient is at home, the MDASI can be completed by Interactive Voice Response (IVR) automated telephone system, electronically through email, or by personal phone call with research staff. Patients have the discretion to elect to forego completion of the MDASI at any time point. All data will be stored in the Department of Lymphoma/Myeloma. MDASI data collection quality and completeness will be monitored by Department of Lymphoma/Myeloma research staff.

7.1.9 FOLLOW-UP ASSESSMENTS

The date of discontinuation and reason(s) for patient discontinuation from the study will be recorded in the chart. All evaluations which are required at the final study visit (and may be scheduled with a +/-3 business day window) must be conducted for each patient who discontinues treatment. Subjects will be followed for toxicity for 30 days after the last dose of study drug(s).

Subjects will be followed via telephone every 3 months for information on progression of disease. The exact date of death will be recorded.

For cutaneous T cell lymphomas, please refer to Appendix 13.

8 ADVERSE EVENTS

8.1 ADVERSE EVENTS DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 should be used to describe the event and for assessing the severity of AEs (see Appendix 4). Any events representing a change in the CTCAE Grade need to be reported on the electronic AE case report form. This includes any change in laboratory values that the investigator feels are clinically significant.

For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

The investigator or attending physician must appraise all abnormal laboratory results for their clinical

significance, documenting with a signature if they are clinically significant or not. If any abnormal laboratory result is considered clinically significant, the investigator or attending physician must provide details about the action taken with respect to the test drug and about the patient's outcome.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

Adverse events and all protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol. For this protocol adverse events will be recorded in the medical record and entered into CORe.

The following are NOT considered AEs:

1. **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
2. **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
3. **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
4. **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

8.2 ADVERSE EVENT CAUSALITY ASSESSMENT

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial

Adverse events will be documented in the medical record and entered into CORe (the electronic case report form for this protocol).

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

Yes: The event is suspected to be related if:

- there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
- there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

No: The event is NOT suspected to be related if:

- the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
- the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
- the event is unlikely to be related to the investigational product(s)

The relationship assessment of the adverse event by the investigator should be documented as follows:

- Unrelated: The AE is clearly NOT related to the treatment.
- Unlikely Related: The AE is doubtfully related to the treatment.
- Possibly Related: The AE may be related to the treatment.
- Probably Related: The AE is likely related to the treatment
- Definitely Related: The AE is clearly related to the treatment.

8.3 SERIOUS ADVERSE EVENT REPORTING (SAE) FOR MD ANDERSON-SPONSORED IND PROTOCOLS

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical

intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Investigator or the IND Sponsor, MDACC IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

8.3.1 OTHER MALIGNANCIES

In addition to all routine adverse event reporting, all other malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

8.4 INVESTIGATOR REPORTING RESPONSIBILITIES

The conduct of the study will comply with all FDA safety reporting requirements. The Investigator has the obligation to report all serious adverse events to the MDACC IRB via the Office of Protocol Research to Oncoceutics and to the IND office. This study will be monitored for compliance by the IND office.

8.4.1 INVESTIGATOR COMMUNICATIONS WITH ONCOCEUTICS

The investigator should inform Oncoceutics of any SAE.

This must be documented on an MD Anderson SAE Form and will be reporting as per Section 8.3. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MD Anderson SAE Form.

The Investigator must inform Oncoceutics via fax at the contact information listed below. Notification should include MD Anderson SAE Form and a cover page. Non-expedited SAEs must be reported to Oncoceutics on a regular basis within 30 days of occurrence in the form of an SAE report.

8.4.1.1 Oncoceutics Drug Safety and Pharmacovigilance

Oncoceutics Contact Information:
Phone: 1-844-ONCORXS (1-844-662-6797); Extension 100
e-mail: pharmacovigilance@oncoceutics.com

8.4.1.2 PREGNANCY REPORTING TO ONCOCEUTICS

Female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to the administration of the first dose of study treatment and agree to use an effective method of contraception during the study and for 90 days following the last dose of study treatment. Contraception must be in place at the latest 2 weeks prior to initiating study treatment and be continued during study drug dose interruption intervals. If a menstrual period in a treated woman does not occur at the anticipated timing a pregnancy test should be performed.

A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Male patients must use an effective barrier method of contraception during the study and for 90 days following the last dose of study treatment if sexually active with a female of childbearing potential.

Pregnancies occurring while a female subject is on ONC201 or within 4 weeks after the subject's last dose of ONC201 or within 3 months of the last dose for a pregnancy in a female partner of a male subject, are considered reportable occurrences. Subjects, spouses, or partners will be followed through the outcome of the pregnancy. If the subject is on ONC201, it is to be discontinued immediately. The pregnancy must be reported by the investigator to the MDACC IRB and IND Offices, to Oncoceutics as per the SAE timelines listed in Sections 8.3 and 8.4.1.

The Investigator will follow the subject until completion of the pregnancy, and must notify Oncoceutics of the outcome as specified below as per the SAE timelines listed in Sections 8.3 and 8.4.1.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Oncoceutics and report the event to the MDACC IRB and IND Offices.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to ONC201 should also be reported.

In the case of a live "normal" birth, Oncoceutics, the MDACC IRB and IND Offices should be advised as soon as the information is available.

8.5 ADVERSE EVENT UPDATES AND IND SAFETY REPORTS

Oncoceutics will notify the Investigator via an IND Safety Report of the following information:
Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, any changes on the investigational brochure or any other safety information that changes the risk/benefit profile of ONC201, respectively, during the conduct of the study.

Any finding from tests in laboratory animals that suggests a significant risk for human subjects; including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Oncoceutics and the IRB, on file.

9 STATISTICS ANALYSIS

9.1 STUDY DESIGN

This will be a single-center, Phase 1/2 clinical trial in patients with refractory or relapsed B cell lymphoma. The feasibility of administrating ONC 201 and the recommended Phase 2 dose (RP2D) will be determined in Phase 1. The tolerability and objective response rate at the RP2D will be evaluated in Phase 2.

9.1.1 PHASE 1

The primary objectives of Phase 1 (dose escalation) are to assess the feasibility, safety and tolerability of ONC 201 and to determine the recommended Phase 2 dose (RP2D) of ONC201. Dose escalation will be guided by standard 3+3 design. ONC201 will be dosed orally once every 3 weeks (Arm A) or 1 week (Arm B). Once the February 9, 2016 amendment is IRB approved, enrollment in Arm A will cease. Patients already enrolled in Arm A will continue to receive ONC201 on the same dose regimen, as stipulated by the protocol (see Section 6.6). No intrapatient dose escalation or cross-over to Arm B is permitted. For each arm, the first cohort of 3 patients will be treated at Dose

Level 1 and evaluated for DLT (defined in section 4.7.2) at the end of first cycle (21 days). The algorithm is as follows: (1) If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose (i.e., 1 out of a total of 6 patients develops a DLT), the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out of 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Given 5 predefined dose levels (given in section 4.4), it is anticipated that the eligible number of patients required for the Phase I part will be up to 30 patients. The MAD or MTD, whichever is reached first in Arm B, will be defined as the RP2D.

9.1.2 PHASE 2

Once the RP2D is determined, an expansion of 30 additional patients will be treated at the RP2D. The primary objective is to confirm the safety and tolerability at the RP2D and to assess tumor response in subjects with advanced lymphoma. The primary endpoint is overall response (OR) defined as either complete response (CR) or partial response (PR) observed in the first 3 treatment cycles. A Bayesian method by Thall et al (1995) will be used for futility and toxicity monitoring. The trial will be stopped early if

$$\Pr(\text{OR rate} < 0.10 \mid \text{data}) > 0.90$$

or

$$\Pr(\text{DLT rate} > 0.30 \mid \text{data}) > 0.90$$

That is, the trial will be stopped early if there is more than a 90% probability that the OR rate is lower than 10% or if there is more than a 90% probability that the DLT rate is higher than 30%. We assume that OR and DLT follow a prior distribution of beta (0.1, 0.9) and beta (0.3, 0.7), respectively. DLTs for phase II toxicity monitoring are the same as those defined in section 4.7.2 for the phase I trial.

The above futility and toxicity monitoring rules will be implemented starting from the 12th patient in Phase 2. The corresponding stopping boundaries are listed in the following Table 9.1 and Table 9.2. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed. For example, if there is no OR in the first 12 patients, stop the trial early due to futility. The trial also needs to be stopped early due to the agent is too toxic if there are 6 or more patients experience DLTs among the first 12 patients.

For cutaneous T cell lymphomas, please note that a separate correlative study (PA18-0191) will be conducted in parallel. PA18-0191 is approved by the MD Anderson IRB and will be co-submitted with protocol 2014-0630.)

Table 9.1: The stopping boundaries of Phase II trial

Number of patients evaluated	Recommend stopping if ≤ Overall Response observed	Recommend stopping if ⩾ Toxicity observed
12	0	6-12
18	0	9-18
24	0-1	11-24
30	Always stop with this many patients	

Table 9.2: The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True OR Rate	True Toxicity Rate	Prob(stop the trial early)	Average number of patients treated
0.05	0.10	0.725	19.2
	0.30	0.767	18.2
	0.50	0.944	14.3
0.10	0.10	0.389	24.3
	0.30	0.483	22.6
	0.50	0.876	15.7
0.20	0.10	0.083	28.7
	0.30	0.223	26.4
	0.50	0.813	17.0

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

External Data Safety Monitoring Board (eDSMB) toxicity and efficacy monitoring

1. Phase I
    a. Toxicity data summary of adverse events and Serious Adverse Events (SAE) with grade and relationship per cohort, treatment related deaths, and will be reviewed by the eDSMB.
    b. The eDSMB review of Phase I toxicity data will be done:
        i. Annually (from the date of first administration of ONC201 to a study participant); and
        ii. Upon completion of Phase I of the study prior to initiation of Phase II of the study.
2. Phase II
    a. Efficacy data Summary as per protocol objectives will be reviewed by the eDSMB.
    b. Toxicity data summary of adverse events and Serious Adverse Events (SAE) with grade and relationship per cohort, treatment related deaths, and will be reviewed by the eDSMB.
    c. The eDSMB review of Phase II toxicity and efficacy data will be done as follows:
        i. Once the Phase II portion of the study has been opened, only 1 patient can be added. Upon enrollment of this patient, the PI should request that the study be closed to new patient entry until approval regarding safety is given from the

eDSMB. This one patient must be fully evaluated for DLT before any additional patients can be added. Update the committee on any toxicity issues that may have occurred with this patient.;

ii. If the Committee has deemed the new dosage as safe, the CNPE status can be lifted and 2 additional patients can be added. The PI should report an update to the eDSMB regarding toxicity for all 3 patients. Again, the protocol should be CNPE during this time period by the PI;

iii. If the eDSMB finds that there has been no change regarding safety, 3 more patients can be enrolled. Again, the study would be CNPE after the enrollment of these 3 patients for eDSMB review of safety for all 6 patients. If there has been no change in safety, the study will re-open to accrual and will be reviewed at this protocol's annual eDSMB review in November 2017.

The investigator is responsible for completing the response/toxicity summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 12 evaluable patients complete 3 treatment cycles and every 6 evaluable patients, thereafter. On every report submission, the information from previously reported patients will need to be updated.

9.1.3 ANALYSIS PLAN

Data analysis will be performed using SAS or R, as appropriate. If RP2D is equal to MTD, statistical analysis on MTD will be conducted on the combined data including both the 6 patients treated at MTD in Phase 1 and up to 30 patients in Phase 2. The OR rate and the DLT rate will be summarized by frequency and 95% confidence interval. Patients who received at least one dose of the treatment drug will be evaluable for toxicity outcomes. Toxicities will be summarized by dose levels, by grade and by their relationship to the treatment. The intent-to-treat patients will be used for the primary efficacy analysis, patients who lost-to-follow up in the first 3 cycles will be treated as failures. The distribution of time-to-event endpoints including OS and PFS will be estimated by the method of Kaplan and Meier Analysis. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

10. RESPONSE CRITERIA

Response definitions for measurable disease from the Revised International Workshop Standardized Response Criteria for non-Hodgkin's Lymphoma will be used (see Appendix 2). Patients will be assessed for response after every 3 cycles of therapy. Patients with stable disease (SD) or better may continue on therapy until disease progression.

For cutaneous T cell lymphomas, please refer to Appendix 5 to 12 for disease classification and response assessments.

10.1 COMPLETE RESPONSE (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

10.2 PARTIAL RESPONSE (PR)

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
   When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

10.3 STABLE DISEASE (SD)

A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

1. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

2. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

10.4 RELAPSED DISEASE (AFTER CR) /PROGRESSIVE DISEASE (AFTER PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extra nodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histological negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CR/unconfirmed (Cru) status, but should be considered partial responses.

APPENDICES

APPENDIX 1

Table of Assessments

Study visits and procedures may be scheduled with a +/- 3 business day window	Screening	Cycle 1 (D1 – 21)						Cycle 2 +		End of Treatment	Follow-up
	Within 28 days*	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	Day 1	Day 2	30 (+/- 3) days post last dose)[17]	
Medical/RX history[1]	X										
Physical exam, ECOG, Height,	X	X		(X)[2]		(X)[2]		X[2]		X	
Vital signs[3]	X	X		X		X				X	
Neurologic assessment[4]	X	X						X[14]		X	
12-lead ECG[14]	X	X[14]	X[14]	X[14]						X	
Hematology[5]	X	X		X		X		X		X	
Full serum chemistries[6]	X	X		X		X		X		X	
Coagulation tests[7]	X									X	
Pregnancy test[8]	X[8]							X		X	
CT chest/abd/pelvis/neck (if applicable)	X							X[9, 10]		X[10]	
CXR	X									X	
Unilateral BMB and aspirate	X[11]							X[11]		X	
Colonoscopy/GI endoscopy	X[12]							X[12]		X	
Other imaging/PET	X							X[9, 10]		X	
ONC 201 administration[13]		X						X			
Blood sample for PK		X[15]						X[19]		X	
Blood/tissue samples for Correlative studies	X[19] (tissue only) (optional)	X[10,16]						X[10,20]		X[10]	
Adverse events		→									
Concomitant medications		→									
Disease status and survival											X[18]
MDASI[21]	X		X		X		X		X[21]	X	X[21]

Footnotes Table of Assessments

(X) Parentheses indicate that the particular test is situational at that time point, as specified in the respective footnote.

* All laboratory assessments are to be done with 14 days of first day of study drug administration, unless otherwise noted.

1. Medical history: prior treatments for lymphoma, significant medical conditions, neuropathy history.
2. Physical examination: review of systems, height at baseline, weight, and if significant weight loss or gain (+/- 10%). Abbreviated PE on Days 8 and 15 of Cycle 1 and Days 1 of each cycle or as clinically indicated.
3. Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature prior to dosing.
4. Neurologic exam: evaluate peripheral neuropathy and/or changes in preexisting neuropathy.
5. Hematology: hemoglobin, hematocrit, WBC with complete manual differential (neutrophils [segmented and bands], lymphocytes, monocytes, eosinophils, basophils), RBCs, platelet count (For Day 1, screening panel may be used if within 24 hours prior to initiation of therapy). Obtain and review on Day 1 of all cycles prior to each dose of ONC 201, on Days 8 and 15 of Cycle 1, and as clinically indicated.
6. Full blood chemistry panel: BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH (for Day 1 screening panel may be used if within 24 hours prior to starting treatment). Obtain and review prior to each dose of ONC201 on Day 1 of each subsequent cycle, on Days 8 and 15 of Cycle 1, and as clinically indicated. Serum β2 microglobulin, viral hepatitis panel including HBsAg, HBcore antibody, HB antibody, Hep C antibody, and GGT at baseline.
7. Coagulation tests: prothrombin time, activated partial thromboplastin time, and international normalized ratio (historical panel may be used if within 14 days prior to starting treatment) 1st day of study drug
8. Pregnancy Test –urine or serum in women of child bearing potential. If a menstrual period in a treated woman does not occur at the anticipated timing a pregnancy test should be performed. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
9. Disease Assessment every other cycle beginning on cycle 3 (i.e. every odd cycle): Obtain bi-dimensional measurements when measurable disease is present unless it becomes PET negative (see response assessment criteria in Appendix 2). Either a PET/CT or a CT can be used before and/or after treatment to assess response.
10. Repeat every other cycle beginning on cycle 3 (i.e. every odd cycle) for the duration of treatment. Perform only those evaluations with known or suspected sites of disease. If no change in persistent mass, a biopsy is to be performed, if feasible.
11. Send baseline bone marrow aspirate for cytogenetics and lymphoma markers. FISH for IgH/cyclin D1 may be required to make a definitive diagnosis if bone marrow is inconclusive. Repeat only if initially positive and send bone marrow aspirate for lymphoma markers. Repeat bone marrow biopsy to confirm CR.
12. Baseline colonoscopy and other GI endoscopies are required only if this is the main area of disease response assessment. If in CR by radiologic evaluation, bone marrow or blood test at any time, do colonoscopy with random biopsy and bone marrow biopsy and PET scan if necessary and possible to confirm CR.
13. ONC201 administration: See Section 4 for study drug administration and Section 6.2 for dose modification guidelines.
14. ECG: baseline, Cycle 1 Day 1 (15 minutes ± 10 minutes, 1 hour ± 15 minutes, and 2 hours ± 30 minutes post-dose), Cycle 1 day 2, Cycle 1 Day 8, and when patients come off study. If indicated due to any cardiac abnormalities, two additional ECGs must be performed at intervals approximately 3 minutes apart.
15. Blood draws taken at baseline, 30 ± 15 minutes, 2 hours ± 30 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 24 ± 1 hour , 48 hours ± 12 hours, 72 ± 12 hours, 96 ± 12 hours, and 168 hours ± 24 hours following administration in the first cycle.
16. Blood draws taken at baseline, 24 ± 1 hour, 48 hours ± 12 hours, and 168 hours ± 24 hours following administration in the first cycle. PD samples can be collected in parallel to PK samples. Each PD blood draw will include one EDTA tube and one tube without anticoagulant.
17. Approximately 30 days (+/- 3) after discontinuation of all study drugs or before start of subsequent treatment (whichever occurs first).
18. Every 3 months via telephone for all subjects for 1 year.

19. For patients with measurable disease, optional core tumor biopsy will be collected at Screening for correlative studies. If patient has had a core biopsy within 12 months, a formalin-fixed paraffin embedded tumor block or slides may be used instead. See Section 7.1.7 for correlative studies to be run.
20. Blood draws taken pre-dose for Cycle 2 and beyond. PD samples can be collected in parallel to PK samples. Tissue samples will be taken at re-staging, as clinically indicated (See footnote 10.)
21. Patients will complete the MDASI starting at screening and weekly until the start of therapy. The MDASI will then be completed weekly beginning on the day after the first dose of study drug for the first 3 cycles of therapy (C1D2, C1D9, C1D16, C2D2, C2D9, C2D16, C3D2, C3D9, C3D16). Patients will then complete the MDASI the day after the start of each cycle of therapy (C4+D2) and approximately 30 days (+/- 3 days) after discontinuation of study drug or before the start of subsequent treatment (whichever occurs first). In follow up, patients will complete the MDASI every 3 months for 1 year. MDASI assessments may be completed on paper or electronic tablet when the patient is in clinic. When the patient is at home, the MDASI can be completed by Interactive Voice Response (IVR) automated telephone system, electronically through email, or by personal phone call with research staff. Patients have the discretion to elect to forego completion of the MDASI at any time point. All data will be stored in the Department of Lymphoma/Myeloma. MDASI data collection quality and completeness will be monitored by Department of Lymphoma/Myeloma research staff.

For cutaneous T cell lymphomas, please refer to additional procedures in protocol PA18-0191 and Appendix 13.

APPENDIX 2

Revised Response Criteria for Malignant Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

APPENDIX 3

ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX 4

NCI CTCAE Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI)
v4.03

Publish Date: June 14, 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 5.

Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS[1]

TNMB Stages	Description of TNMB
Skin[*]	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node[†]	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive

TNMB Stages	Description of TNMB
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative

TNMB Stages	Description of TNMB
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions[1] to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.
‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood

Appendix 6

Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or
	New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or
	Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.

*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.
†Whichever criterion occurs first.

Olsen E. Vonderheid E., ,Pimpinell N, et al Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORT). Blood. 2007: 110(6) 1713-1722

Appendix 7

Response in Lymph Nodes*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or
	Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or
	Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Peripheral and central lymph nodes.
†Whichever criterion occurs first.

Appendix 8

Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or
	> 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or
	Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*As determined by absolute numbers of neoplastic cells/μL.
†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
§Whichever occurs first.

Appendix 9

Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or
	New organ involvement or
	Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Whichever criterion occurs first

Appendix 10

Skin Assessment and Scoring

NOTE. mSWAT score equals summation of total patch, plaque and tumor

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

Patch-Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present. Total sum is multiplied by 1 for mSWAT (modified Severity Weighted Assessment Tool)

Plaque Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present. Total sum is multiplied by 2 for mSWAT

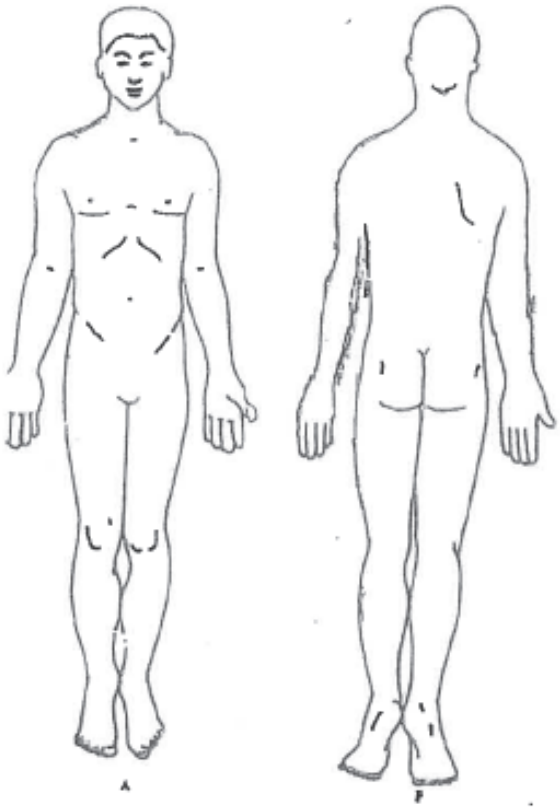
Tumor ‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth. Total sum is multiplied by 4 for mSWAT.

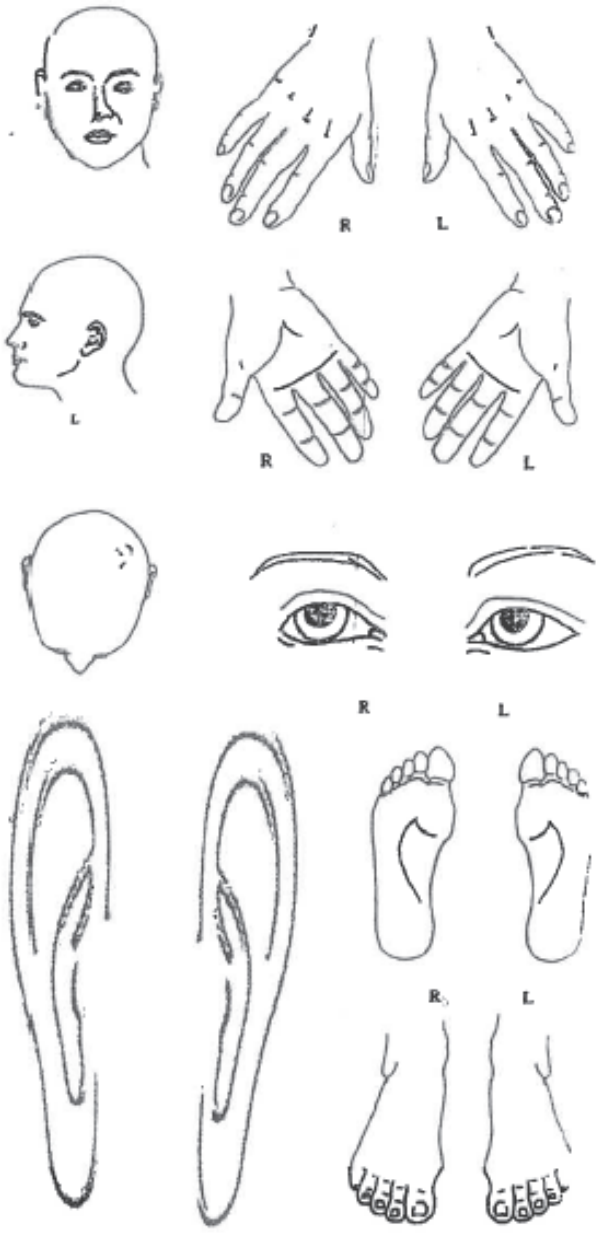
Appendix 11 Body Surface Area Assessment Note

Body-Surface Area Assessment Note

Patient
ACCT#
DOB

MDA #
Print Date
PC SEX Location





Area	%BSA for region	% BSA Patch	% BSA Plaque	% BSA Tumor
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower leg	14			
Feet	7			
Total	100			

Total BSA involvement % BSA Patch _____
% BSA Plaque _____
% BSA Tumor _____
Total BSA involvement % BSA = _____

Signature/Credentials/ID#/Date/Time _____

Body Surface Area Assessment Note Page 1 of 1
File Under: Progress Notes

INS999064 12/03 Revised 04/13

Appendix 12 CTCL Assessment and Response

Response criteria for patients with CTCL will be determined from the composite scores (Global Response) of four categories – skin, nodes, visceral and blood (Appendix 5-9) the criteria for response and staging is from ISCL/EORTC recommendation (Olsen, 2011).Skin assessment is done by modified skin weighted assessment tool(Appendix 10 & 11). Node and visceral assessment is determined by CT scan. A node biopsy at screening will be done on patients with nodes> 1.5 cm and clinically suspicious for disease. Blood is assessed by peripheral blood flow cytometry.

1) Complete Response (CR) is the complete absence of all clinical disease in all involved categories

2) Partial response skin (PR) is either CR or PR and

    a. All categories do not have a CR or not involved (NI) and no category has progressive disease or
    b. No category has progressive disease (PD) and if any category is involved at baseline, at least one has a CR or PR

3) Stable disease skin (SD) is either PR or SD

    a. No category has progressive disease and if any category is involved at baseline, no CR or PR
    b. CR/NI/PR/SD in any category and no category has PD

4) Progressive disease is PD in any category

5) Relapse-recurrence disease in prior CR is relapse in any category

APPENDIX 13

Table of Assessments for Cutaneous T-Cell Lymphoma

Study visits and procedures may be scheduled with a +/- 3 business day window	Screening	Cycle 1 (D1 – 21)						Cycle 2+		End of Treatment	Follow-up
	Within 28 days*	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	Day 1	Day 2	30 (+/- 3) days post last dose)[17]	
Medical RX history[1]	X										
Physical exam, ECOG, Height	X	X		(X)[2]		(X)[2]		X[2]		X	
Vital signs[3]	X	X		X		X		X		X	
Neurologic assessment[4]	X	X						X		X	
12-lead ECG[14]	X	X[14]	X[14]	X[14]						X	
Hematology[5]	X	X		X		X		X		X	
Full serum chemistries[6]	X	X		X		X		X		X	
Coagulation test[7]	X									X	
Pregnancy test[8]	X									X	
CT chest/abd/pelvis/neck	X							X[22]		X	
CXR	X									X	
mSWAT	X	X						X[23]		X	
Peripheral blood flow cytometry	X							X[24]		X	
Photographs		X						X[23]		X	
Pruritus	X	X						X[23]		X	
ONC 201 administration[13]		X						X		X	
Blood sample for PK		X[15]						X		X	
Optional blood/tissue samples for Correlative studies		X						X[25]		X	
Adverse events		X	X	X	X	X	X	X	X	X	
Concomitant medications		X	X	X	X	X	X	X	X	X	
Disease status and survival											X[18]
MDASI[21]	X		X		X		X		X	X	X[21]

Parentheses indicate that the particular test is situational at that time point, as specified in the respective footnote.

* All laboratory assessments are to be done with 14 days of first day of study drug administration, unless otherwise noted.

1. Medical history: prior treatments for lymphoma, significant medical conditions, neuropathy history.
2. Physical examination: review of systems, height at baseline, weight, and if significant weight loss or gain (+/- 10%). Abbreviated PE on Days 8 and 15 of Cycle 1 and Days 1 of each cycle or as clinically indicated.
3. Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature prior to dosing.
4. Neurologic exam: evaluate peripheral neuropathy and/or changes in preexisting neuropathy.
5. Hematology: hemoglobin, hematocrit, WBC with complete manual differential (neutrophils [segmented and bands], lymphocytes, monocytes, eosinophils, basophils), RBCs, platelet count (For Day 1, screening panel may be used if within 24 hours prior to initiation of therapy). Obtain and review on Day 1 of all cycles prior to each dose of ONC 201, on Days 8 and 15 of Cycle 1, and as clinically indicated.

6. Full blood chemistry panel: BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH (for Day 1 screening panel may be used if within 24 hours prior to starting treatment). Obtain and review prior to each dose of ONC201 on Day 1 of each subsequent cycle, on Days 8 and 15 of Cycle 1, and as clinically indicated. Serum β2 microglobulin, viral hepatitis panel including HBsAg, HBcore antibody, HB antibody, Hep C antibody, and GGT at baseline.
7. Coagulation tests: prothrombin time, activated partial thromboplastin time, and international normalized ratio (historical panel may be used if within 14 days prior to starting treatment) 1st day of study drug
8. Pregnancy Test –urine or serum in women of child bearing potential. If a menstrual period in a treated woman does not occur at the anticipated timing a pregnancy test should be performed. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
9. Disease Assessment every other cycle beginning on cycle 3 (i.e. every odd cycle): Obtain bi-dimensional measurements when measurable disease is present unless it becomes PET negative (see response assessment criteria in Appendix 2). Either a PET/CT or a CT can be used before and/or after treatment to assess response.
10. Repeat every other cycle beginning on cycle 3 (i.e. every odd cycle) for the duration of treatment. Perform only those evaluations with known or suspected sites of disease. If no change in persistent mass, a biopsy is to be performed, if feasible.
11. Send baseline bone marrow aspirate for cytogenetics and lymphoma markers. FISH for IgH/cyclin D1 may be required to make a definitive diagnosis if bone marrow is inconclusive. Repeat only if initially positive and send bone marrow aspirate for lymphoma markers. Repeat bone marrow biopsy to confirm CR.
12. Baseline colonoscopy and other GI endoscopies are required only if this is the main area of disease response assessment. If in CR by radiologic evaluation, bone marrow or blood test at any time, do colonoscopy with random biopsy and bone marrow biopsy and PET scan if necessary and possible to confirm CR.
13. ONC201 administration: See Section 4 for study drug administration and Section 6.2 for dose modification guidelines.
14. ECG: baseline, Cycle 1 Day 1 (15 minutes ± 10 minutes, 1 hour ± 15 minutes, and 2 hours ± 30 minutes post-dose), Cycle 1 day 2, Cycle 1 Day 8, and when patients come off study. If indicated due to any cardiac abnormalities, two additional ECGs must be performed at intervals approximately 3 minutes apart.
15. Blood draws taken at baseline, 30 ± 15 minutes, 2 hours ± 30 minutes, 4 hours ± 30 minutes, 6 hours ± 30 minutes, 24 ± 1 hour , 48 hours ± 12 hours, 72 ± 12 hours, 96 ± 12 hours, and 168 hours ± 24 hours following administration in the first cycle.
16. Blood draws taken at baseline, 24 ± 1 hour, 48 hours ± 12 hours, and 168 hours ± 24 hours following administration in the first cycle. PD samples can be collected in parallel to PK samples. Each PD blood draw will include one EDTA tube and one tube without anticoagulant.
17. Approximately 30 days (+/- 3) after discontinuation of all study drugs or before start of subsequent treatment (whichever occurs first).
18. Every 3 months via telephone for all subjects for 1 year.
19. For patients with measurable disease, optional core tumor biopsy will be collected at Screening for correlative studies. If patient has had a core biopsy within 12 months, a formalin-fixed paraffin embedded tumor block or slides may be used instead. See Section 7.1.7 for correlative studies to be run.
20. Blood draws taken pre-dose for Cycle 2 and beyond. PD samples can be collected in parallel to PK samples. Tissue samples will be taken at re-staging, as clinically indicated (See footnote 10.)
21. Patients will complete the MDASI starting at screening and weekly until the start of therapy. The MDASI will then be completed weekly beginning on the day after the first dose of study drug for the first 3 cycles of therapy (C1D2, C1D9, C1D16, C2D2, C2D9, C2D16, C3D2, C3D9, C3D16). Patients will then complete the MDASI the day after the start of each cycle of therapy (C4+D2) and approximately 30 days (+/- 3 days) after discontinuation of study drug or before the start of subsequent treatment (whichever occurs first). In follow up, patients will complete the MDASI every 3 months for 1 year. MDASI assessments may be completed on paper or electronic tablet when the patient is in clinic. When the patient is at home, the MDASI can be completed by Interactive Voice Response (IVR) automated telephone system, electronically through email, or by personal phone call with research staff. Patients have the discretion to elect to forego completion of the MDASI at any time point. All data will be stored in the Department of Lymphoma/Myeloma. MDASI data collection quality and completeness will be monitored by Department of Lymphoma/Myeloma research staff.

22 Repeat every third cycle of therapy beginning at Cycle 4 for patients N^2 and N^3 at screening. Patients < N^2 within 1 week of first skin response or to confirm progression in nodes.
23 mSWAT, Photographs and Pruritus at each Day 1.
24 Repeat every third cycle beginning at Cycle 4 for those patients B^1 or B^2 at screening
25 Optional skin biopsy and blood at Cycle 2 Day 1 pre-dose

11. REFERENCES

Allen JE, Krigsfeld G, Mayes PA, Patel L, Dicker DT, Patel AS, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction and potent anti-tumor effects. Science Translational Medicine. 2013.

Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 117(19):5019–5032, 2011.

Cheson BD, Horning SJ, Coiffier B, et al. Hematologic Oncology: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. JCO 1244, 1999.

Edwards LA, Verreault M, Thiessen B, Dragowska WH, Hu Y, Yeung JHF, et al. Combined inhibition of the phosphatidylinositol 3-kinase/Akt and Ras/mitogen-activated protein kinase pathways results in synergistic effects in glioblastoma cells. Molecular Cancer Therapeutics 5(3):645-54, 2006.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45(2):228-47, 2009.

Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A ,et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory, 2006.

Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a Standard Regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's Lymphoma N Engl J Med 328:1002-6, 1993.

Forstpointner R, Unterhalt M, Dreyling M, Bock HP, Repp R, Wandt H, Pott C, Seymour JF, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 108(13):4003–4008, 2006.

Goodsell DS. The Molecular Perspective: The ras Oncogene. The Oncologist 4(3):263-4, 1999.

Goy A, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 20(3): 520-5, 2009.

Hamlin PA, Zelenetz AD, Kewalramani T, Qin J, Satagopan JM, Verbel D, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood 102:1989-96, 2003.

He L, Jang JH, Choi HG, Lee SM, Nan MH, Jeong SJ, Dong Z, Kwon YT, Lee KS, Lee KW, Chung

JK, Ahn JS, Kim BY. Oligomycin A enhances apoptotic effect of TRAIL through CHOP-mediated death receptor 5 expression. Mol Carcinog. 2013 Feb; 52(2):85-93.

Herrmann A, Hoster E, Zwingers T, Brittinger G, Engelhard M, Meusers P, Reiser M, Forstpointner R, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol 27(4):511–518, 2009.

Hiddemann W, Unterhalt M, Herrmann R, Woltjen HH, Kreuser ED, Trumper L, Reuss-Borst M, Terhardt-Kasten E, et al. Mantle-cell lymphomas have more widespread disease and a slower response to chemotherapy compared with follicle-center lymphomas: Results of a prospective comparative analysis of the German Low-Grade Lymphoma Study Group. J Clin Oncol 16(5):1922– 1930, 1998.

Ishizawa J and Andreeff M, unpublished data, 2014.

Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat Rev Cancer 7(10):750–762, 2007.

Kahl BS, Longo WL, Eickhoff JC, Zehnder J, Jones C, Blank J, McFarland T, Bottner W, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression free survival in mantle cell lymphoma: a pilot study from the Wisconsin Oncology Network. Ann Oncol 17(9):1418–1423, 2006.

Kahl BS1, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood. 2016 Apr 28;127(17):2055-63.

Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 103:3684-8, 2004.

Khouri IF, Saliba RM, Hosing C, Okoroji GJ, Acholonu S, Anderlini P, Couriel D, De Lima M, et al. Concurrent administration of high-dose rituximab before and after autologous stem-cell transplantation for relapsed aggressive B-cell non-Hodgkin's lymphomas. J Clin Oncol 23(10):2240–2247, 2005.

Khouri IF, Lee MS, Saliba RM, Jun G, Fayad L, Younes A, Pro B, Acholonu S, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 21(23):4407–4412, 2003.

Komatsu S, Miyazawa K, Moriya S, Takase A, Naito M, Inazu M, Kohno N, Itoh M, Tomoda A. Clarithromycin enhances bortezomib-induced cytotoxicity via endoplasmic reticulum stress-mediated CHOP (GADD153) induction and autophagy in breast cancer cells. Int J Oncol. 2012 Apr; 40(4):1029-39.

Leonard JP, Schattner EJ, Coleman M. Biology and management of mantle cell lymphoma. Curr Opin Oncol 13(5):342–347, 2001.

Li H, Chang G, Wang J, Wang L, Jin W, Lin Y, Yan Y, Wang R, Gao W, Ma L, Li Q, Pang T. Cariporide Sensitizes Leukemic Cells to TRAIL by Up-regulation of Death Receptor 5 via ER

stress-CHOP dependent Mechanism. Leuk Lymphoma. 2013 Nov 4.

Martín A, Conde E, Arnan M, Canales MA, Deben G, Sancho JM, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: The influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 93:1829-36, 2008.

Martin P, Chadburn A, Christos P, Furman R, Ruan J, Joyce MA, Fusco E, Glynn P et al. Intensive treatment strategies may not provide superior outcomes in mantle cell lymphoma: overall survival exceeding 7 years with standard therapies. Ann Oncol
19(7):1327–1330, 2008.

Perry AR, Goldstone AH. High-dose therapy for diffuse large-cell lymphoma in first remission. Ann Oncol 9:1:9-14, 1998.

Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomized controlled trial by the MabThera International Trial (MInT) Group.
Lancet Oncol 7:379-91, 2006.

Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, Pro B, McLaughlin P, Younes A, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol 23(28):7013–7023, 2005.

Rosenwald A, Wright G, Wiestner A, Chan WC, Connors JM, Campo E, Gascoyne RD, Grogan TM, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 3(2):185–197, 2003.

Salaverria I, Royo C, Carvajal-Cuenca A, Clot G, Navarro A, Valera A, Song JY, Woroniecka R, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. Blood 121(8): 1394-402, 2013.

Senderowicz AM. Information Needed to Conduct First-in-Human Oncology Trials in the United States: A View from a Former FDA Medical Reviewer. Clinical Cancer Research. 2010 March 15, 2010;16(6):1719-25.

Shimizu T, Tolcher AW, Papadopoulos KP, Beeram M, Rasco DW, Smith LS, et al. The Clinical Effect of the Dual-Targeting Strategy Involving PI3K/AKT/mTOR and RAS/MEK/ERK Pathways in Patients with Advanced Cancer. Clinical Cancer Research. 2012 April 15, 2012;18(8):2316-25.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. WHO classification of tumours of haemotopoietic and lymphoid tissues, 4th edn. WHO Press, Geneva (Switzerland), 2008.

Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med 14(4):357-379, 1995. PMID: 7746977.

Vellenga E, van Putten WL, van't, Veer MB, Zijlstra JM, Fibbe WE, van Oers MH, et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+NHL: A prospective randomized HOVON trial. Blood 111:537-43, 2008.

Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 369:507-516, 2013.

Weisenburger DD, Kim H, Rappaport H. Mantle-zone lymphoma: a follicular variant of intermediate lymphocytic lymphoma. Cancer 49(7):1429–1438, 1982.

Yang J-Y, Zong CS, Xia W, Yamaguchi H, Ding Q, Xie X, et al. ERK promotes tumorigenesis by inhibiting FOXO3a via MDM2-mediated degradation. Nat Cell Biol. 2008;10(2):138-48.

Zhou Y, Wang H, Fang W, Romaguer JE, Zhang Y, Delasalle KB, Kwak L, Yi Q, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 113(4):791–798, 2008.