**UWCCC Protocol #: UW17107**

**ClinicalTrials.gov Identifier:** NCT03733119

IND#: 138830

**TITLE: Phase 2 study of ONC201 with a methionine-restricted diet in patients with metastatic triple negative breast cancer**

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**INVESTIGATOR SIGNATURE PAGE**

Protocol Number: UW17107
Protocol Title: Phase 2 study of ONC201 with a methionine-restricted diet in patients with metastatic triple negative breast cancer

I have read this protocol and agree to conduct this trial in accordance with this document, good clinical practice, the Declaration of Helsinki, and all applicable laws and regulations. I understand that it must be reviewed and approved for conduct by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

_____ _____
Principal Investigator Name (Printed) Title

_____ _____
Principal Investigator Signature Date

Site Name and Address:

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**SYNOPSIS**

| | |
|---|---|
| **TITLE** | Phase 2 study of ONC201 with a methionine-restricted diet in patients with metastatic triple negative breast cancer |
| **SHORT TITLE** | ONC201 and methionine-restricted diet in TNBC |
| **PHASE** | II |
| **STUDY OBJECTIVES** | Primary Objective:<br>• To determine objective response rate (ORR) to ONC201 with a methionine-restricted diet in patients with metastatic triple negative breast cancer (TNBC).<br>Secondary Objectives:<br>• To determine progression-free survival (PFS) to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.<br>• To determine clinical benefit rate (complete or partial response plus stable disease) (CBR) at 4 months to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.<br>• To determine overall survival (OS) to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.<br>• To assess metabolic indices in patients with metastatic TNBC treated with ONC201 and a methionine-restricted diet.<br>• To assess the expression of TRAIL receptor in circulating tumor cells (CTCs) prior, during and upon progression in patients with metastatic TNBC treated with ONC201 with a methionine-restricted diet.<br>Exploratory Objective:<br>• To determine time to development of brain metastases or worsening of brain metastases in patients with metastatic TNBC treated with ONC201 with a methionine-restricted diet. |
| **STUDY DESIGN** | Patients with metastatic TNBC will be enrolled in a single-arm study evaluating ONC201 with a methionine-restricted diet. |
| **BRIEF ELIGIBILITY CRITERIA** | 1. Metastatic or unresectable TNBC (ER<10%, PR<10% and HER2 negative either by IHC or in situ hybridization method by ASCO-CAP guidelines).<br>2. Measurable disease by RECIST 1.1.<br>3. Any number of prior lines of systemic therapy for metastatic disease is allowed.<br>4. ECOG PS of 0 or 1.<br>5. No active CNS metastatic disease; subjects with prior definitive treatment of their CNS disease by surgical resection, SBRT or |

| | |
|---|---|
| | WBRT >28 days ago will be eligible if asymptomatic and off systemic steroids.<br>6. Life expectancy of greater than 12 weeks.<br>7. Normal organ and marrow function as defined per protocol definitions.<br>8. Excludes patients who follow a vegan or vegetarian diet |
| **STATISTICAL CONSIDERATIONS** | The primary objective is to evaluate efficacy of ONC201 with a methionine-restricted diet in metastatic TNBC. The study is designed as a single-arm phase II trial. The primary endpoint is ORR. Secondary endpoints include CBR, PFS, OS, safety, metabolic indices and CTC TRAIL-receptor expression. The null hypothesis is that the probability of ORR is no more than 0.1, *i.e.*, $H_0$: $p \leq 0.1$, and the alternative hypothesis is $H_1$: $p \geq 0.25$. In this single arm study, a Simon's two stage design will be utilized. The null hypothesis that the true ORR is 0.1 will be tested against a one-sided alternative. The study will be powered to detect an ORR of 25% with the combination of ONC201 with a methionine-restricted diet, using a power of 80% and a type I error rate of 10%. The first stage sample size will be 13. After testing the combination on 13 subjects in the first stage, the trial will be terminated if 1 or fewer subjects respond. If the trial goes on to the second stage, a total of 34 subjects will be studied (i.e. additional 21 subjects will be recruited). If the total number responding or having ORR is less than or equal to 5, the combination of ONC201 with a methionine-restricted diet will be rejected.<br>Time to event outcomes such as PFS and OS will be analyzed using Kaplan-Meier method and Cox proportional hazards regression. |
| **TOTAL NUMBER OF SUBJECTS** | Number of subjects in the phase II study: 34 |
| **ESTIMATED ENROLLMENT PERIOD** | Estimated 30 months |
| **ESTIMATED STUDY DURATION** | Estimated 36 months |

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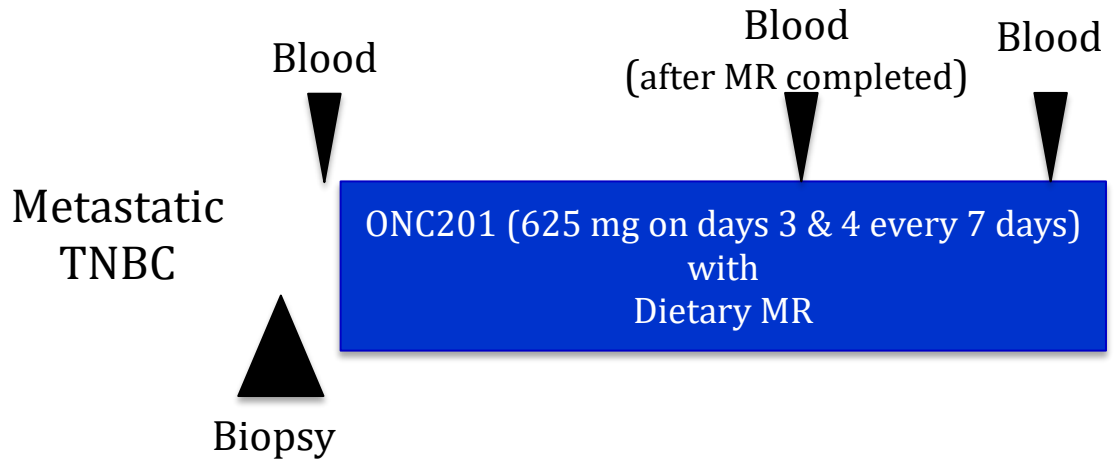
**STUDY SCHEMA**

WEEKLY SCHEDULE:




ONC201 is taken weekly on days 3 and 4 at 625mg by mouth.
*Optional tumor biopsy is obtained at baseline.
#Blood for circulating tumor cells (black triangle) will be taken at baseline, **on day 5 of cycle 2,** and at end of treatment.
MR (methionine-restricted diet) will be followed days 1 through 5 weekly.

**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ANC | absolute neutrophil count |
| ALT | alanine aminotransferase |
| AQUA | automated quantitative analysis |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| BCSC | breast cancer stem cell |
| BSA | body surface area |
| CBC | complete blood count |
| CBR | clinical benefit rate |
| cm | centimeter |
| CMP | comprehensive metabolic panel |
| CNS | central nervous system |
| CR | complete response |
| CTC | circulating tumor cell |
| CTCAE | (NCI) Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| CYP | cytochrome P450 |
| dL | deciliter |
| DOR | duration of response |
| DSMC | Data and Safety Monitoring Committee |
| DSMP | Data and Safety Monitoring Plan |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ER | endoplasmic reticulum |
| ER | estrogen receptor |
| ERK | extracellular regulated signal kinase |
| FDA | Food and Drug Administration |
| h | hour |
| Hcy | homocysteine |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| HFSR | hand-foot skin reaction |
| HIPAA | Health Insurance Portability and Accountability Act |
| HPMC | hydroxypropyl methylcellulose |
| IHC | immunohistochemistry |
| IND | Investigational New Drug |

| | |
|---|---|
| IRB | institutional review board |
| ISR | integrated stress response |
| kg | kilogram |
| lbs | pounds |
| LC-MS | liquid chromatography–mass spectrometry |
| LLN | lower limit of normal |
| mg | milligram |
| min | minute |
| mL | milliliter |
| $mm^3$ | cubic millimeters |
| MR | methionine restriction |
| MTA | 5'-methythioadenosine |
| NCI | National Cancer Institute |
| MTD | maximum tolerated dose |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PI3K | phosphoinositide 3-kinase |
| PK | pharmacokinetics |
| PPE | polypropylene |
| PR | partial response |
| PR | progesterone receptor |
| PS | performance status |
| PSR | Protocol Summary Report |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | recommended phase II dose |
| SAE | serious adverse event |
| SAH | S-adenosylhomocysteine |
| SAM | S-adenosylmethionine |
| SD | stable disease |
| SOP | standard operating procedure |
| TNBC | triple negative breast cancer |
| ULN | upper limit of normal |
| US | United States |
| wt | weight |
| WON | Wisconsin Oncology Network |

# 1. BACKGROUND AND RATIONALE

## 1.1 Disease background

Breast cancer remains an important global health issue. One of eight U.S. women is diagnosed with breast cancer during her lifetime[1]. The American Cancer Society estimates that 234,190 new cases of invasive breast cancer will be diagnosed in the United States in 2015 with 40,730 deaths[2] Triple-negative breast cancer (TNBC) constitutes approximately 15% of breast cancers and lacks expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). TNBC is associated with African-American and Hispanic race, younger age at diagnosis, advanced stage, high mitotic index, and BRCA1 mutations[3-7]. Due to the absence of any targeted therapies, cytotoxic chemotherapy remains the mainstay of medical treatment for TNBC, but outcomes are poor compared with other subtypes[8, 9]. Median survival for women with advanced TNBC remains a dismal 13 months[9]. Improved understanding of this disease to advance our treatment approaches are urgently required.

## 1.2 Targeting pro-apoptotic TRAIL receptors in cancer

TRAIL and agonistic humanized monoclonal antibodies (mAbs) targeting its death receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5) have garnered great interest as cancer therapeutics because they preferentially activate apoptosis in transformed cells independent of p53 status and exhibit broad antitumor activity in preclinical models[10]. We demonstrated that a humanized agonistic TRAIL-R2 mAb suppressed lung metastases in a murine TNBC model[11]. Although TRAIL and agonistic TRAIL-R2 mAbs have been demonstrated to be safe in clinical trials, they have failed to demonstrate a therapeutic benefit in advanced solid malignancies[12-14].

## 1.3 Selective metabolic vulnerability of tumors and cancer stem cells to methionine restriction (MR)

Diverse tumors are selectively vulnerable to specific amino acid deficiencies, including methionine[15]. Methionine depletion inhibits cell cycle progression and induces apoptosis in many transformed cells, but not normal cells[16, 17]. Dietary MR inhibits tumor growth in diverse murine models[18]. Intriguingly, we have observed that breast cancer stem cells (BCSCs), rare stem-like cells within breast tumors that likely contribute to chemotherapy-resistance and metastasis[19], are dependent on methionine for cell survival as determined by mammosphere assays and BCSC markers ($CD44^{hi}/CD24^{low}$) (**Fig. 1**). Eradication of chemotherapy-resistant BCSCs is likely to be critical to prevent relapses/recurrence[19]. Hence, the tumor-selectivity of MR, coupled with its activity against BCSCs, make it an attractive cancer therapy and distinguish it from cytotoxic agents. Methionine restriction also reduces adiposity, improves metabolic indices and extends lifespan in rodents[20-22]. Although methionine plays a critical role in protein synthesis and methylation of nucleic acids and proteins, the mechanisms underlying the “methionine dependence” of cancer is poorly understood[18].

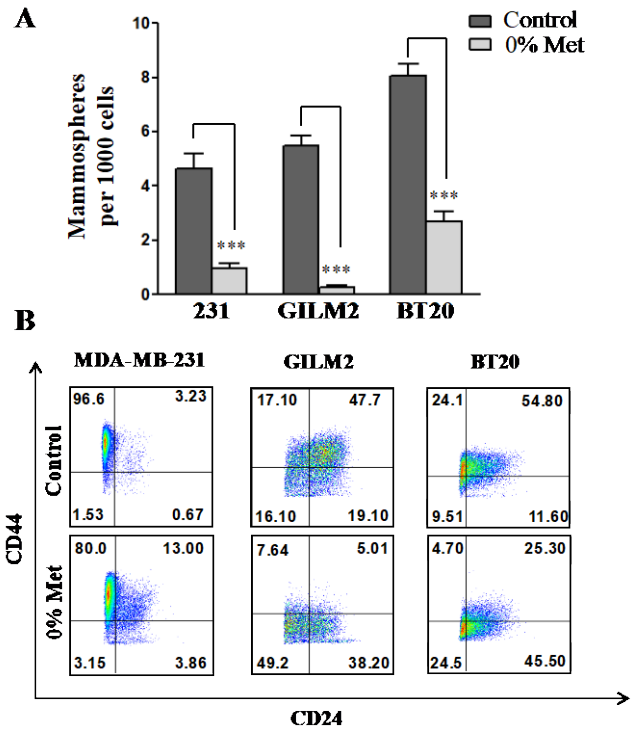



**Fig. 1. MR inhibits breast cancer stem cells. A)** MDA-MB-231 (231), GILM2 and BT20 TNBC cells were grown as mammospheres in 0% methionine (Met) or control media. ***$P < 0.001$. **B**) The CD44 and CD24 populations of cells grown in 0% Met or control media was determined by flow cytometry (percentage of cells in each quadrant is indicated).

## 1.4 Methionine deprivation primes TNBC to pro-apoptotic therapy

We recently demonstrated that methionine deprivation exposes a targetable vulnerability TNBC cells by enhancing TRAIL receptor-2 (TRAIL-R2) mRNA levels and cell surface expression (**Fig. 2**).

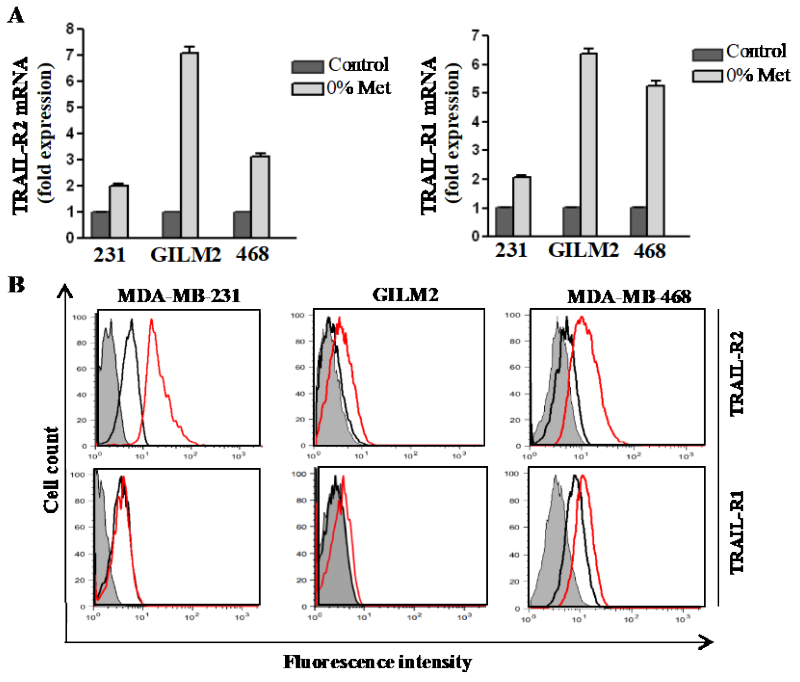



**Fig. 2. MR induces TRAIL receptor expression. A)** Normalized mRNA levels of TRAIL-R2 and TRAIL-R1 in MDA-MB-231 (231), GILM2 and MDA-MB-468 (468) TNBC cells grown in 0% Met or control media for 72 h. **B**) Cell surface expression of TRAIL-R2 or TRAIL-R1 determined by flow cytometry in TNBC cells grown in 0% Met (red line) or control media (black line) for 72 h. Gray bar is IgG negative control. Taken from our published work[23].

The resulting increased TRAIL-R2 expression renders TNBC cells susceptible to TRAIL-R2 agonists such as the humanized TRAIL-R2 mAb lexatumumab (**Fig. 3**). Strikingly, this metabolic priming

of MR is specific for TNBC cells and does not occur in non-transformed cells or in other breast cancer subtypes[23].

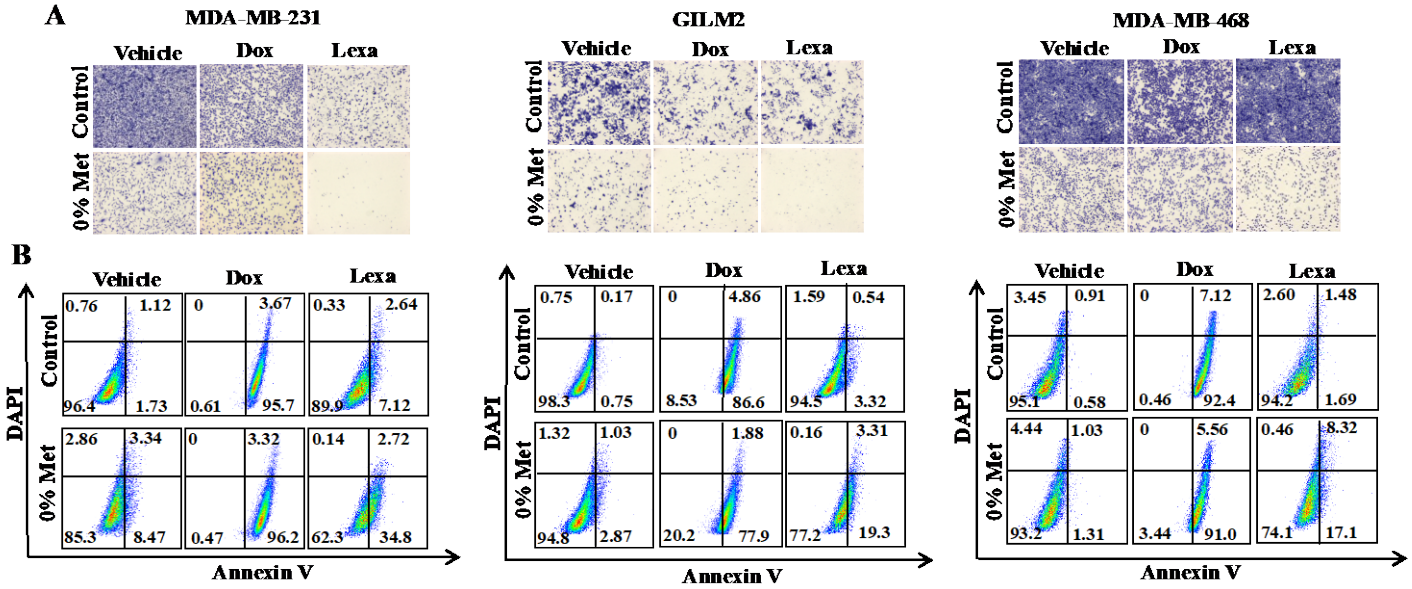



**Fig. 3. MR sensitizes TNBC cells to the TRAIL-R2 agonist lexatumumab. A)** Crystal violet assay and **B)** Annexin V labeling of TNBC cells grown in 0% Met or control media and treated with vehicle, doxorubicin (Dox) or lexatumumab (Lexa) for 48 h (**A**) or 6 h (**B**, percentage of cells in each quadrant is indicated). Taken from our published work[23].

We also demonstrated that a brief exposure to dietary MR is well tolerated by mice and enhances the antitumor activity of lexatumumab against mammary tumors and lung metastases in an orthotopic TNBC model (**Fig. 4**). Our current findings point to methionine deprivation as a novel nutritional intervention to metabolically prime TNBC to respond to a pro-apoptotic TRAIL-R2 mAb, thereby enhancing their therapeutic efficacy**.** Moreover, phase I and phase II trials of a methionine-free diet alone or in combination with chemotherapy in patients with metastatic or recurrent solid tumors have confirmed the safety and tolerability of methionine deprivation (up to 39 weeks)[24, 25].

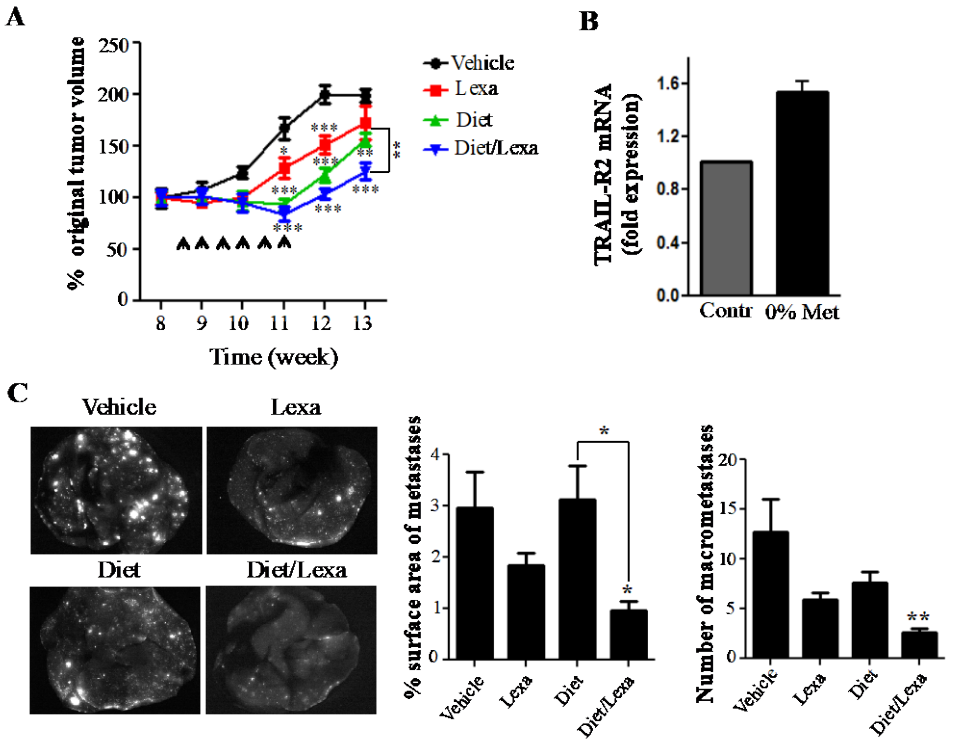



**Fig. 4. Dietary MR enhances the antitumor effects of the TRAIL-R2 agonist lexatumumab in a mouse TNBC model. A)** Female NSG mice with MDA-MB-468 mammary tumors (10 mice per group) were treated with vehicle and control diet, lexatumumab (Lexa) and control diet, MR (Diet) or MR and lexatumumab (Diet/Lexa) for 3 weeks (indicated by arrows). % original mammary tumor volume is shown. **B)** Real-time PCR analysis of TRAIL-R2 mRNA in mammary tumors. **C)** Fluorescent whole lung images. Metastatic tumor burden was measured by % surface of lung occupied by metastases and number of macrometastases. **P* < 0.05, ***P* < 0.01, and ****P* < 0.001. Taken from our published work [23].

## 1.5 ONC201

ONC201 (TIC10) is a first-in-class small molecule that activates apoptosis in tumor but not normal cells in a p53-independent manner. In solid tumors studies, ONC201 indirectly inactivates the Ras effector target kinases, Akt and ERK[26]. Akt and ERK are well-established targets for novel oncology drug development due to their cooperative pro-apoptotic effects. The downside of drugs with high selectivity for single targets that have been developed as a result of the pursuit of these pathways include a lack of high selectivity between malignant and normal cells and as a result, a high toxicity from the attempt to simultaneously inhibit both kinases. In addition, there is a frequent and often rapid development of resistance. The dual inactivation of Akt and ERK by ONC201 results in broad-spectrum cytotoxic activity that includes activation of apoptosis and other downstream antitumor effects to produce a potent antitumor response.

Hematological malignancies are highly sensitive to endoplasmic reticulum (ER) stress, which results from an overload of misfolded proteins in the ER. ER stress can be triggered by multiple mechanisms and has been targeted by several

pharmacological agents indicated for cancer. This includes HSP90 and proteasome inhibitors such as bortezomib, which is approved by the FDA to treat multiple myeloma and mantle cell lymphoma. Robust activation of the pro-apoptotic arm of ER stress in tumor cells has been observed in response to ONC201 treatment in both solid and liquid tumors. Inactivation of Akt and ERK signaling has been linked to ER stress induction in several cancer cell lines.

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. 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.

### 1.5.1 **Preclinical Efficacy**

ONC201 induces broad-spectrum cell death in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that render resistance to chemotherapies and targeted agents. ONC201 induces caspase-mediated apoptosis in cancer cell lines and exhibits broad-spectrum cytotoxicity in vitro. ONC201 displays single agent anti-tumor effects (**Fig. 5**) 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. Importantly, MR robustly sensitizes TNBC cells to ONC201 (**Fig. 6**).

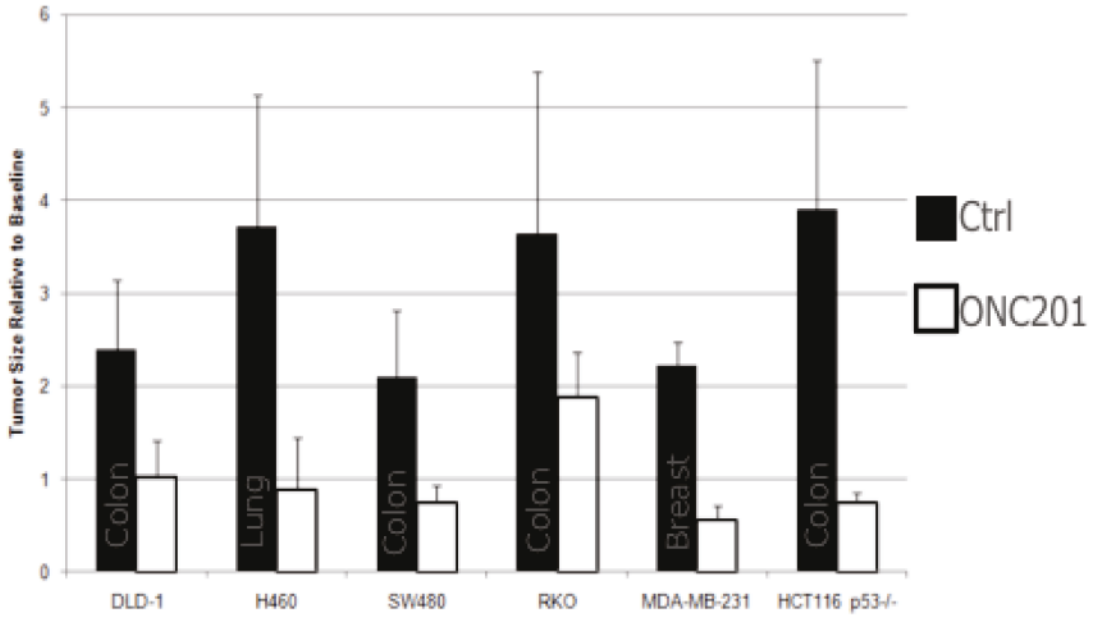



**Figure 5 ONC201 antitumor activity in subcutaneous xenografts.** Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and is relative to the tumor size on the day of administration.

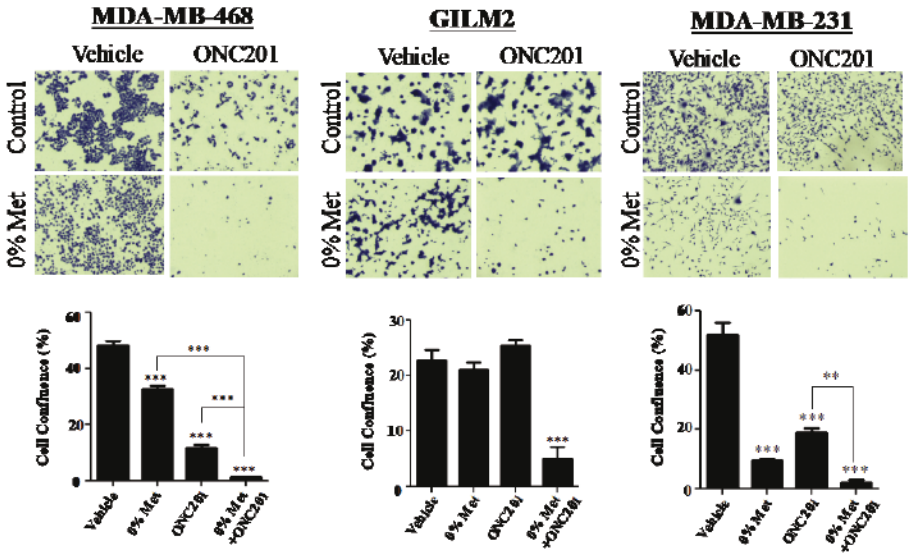



**Fig. 6. MR sensitizes TNBC cells to ONC201.** The indicated TNBC cells were grown in control or 0% methionine media and treated with vehicle or 5 μM ONC201 for 72 h. Viable cells were stained with crystal violet, and the % confluence of viable cells was determined. $^{**}P < 0.01$ or $^{***}P < 0.001$ *vs.* vehicle or the indicated comparison.

### 1.5.2 **Mechanism of Action**

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

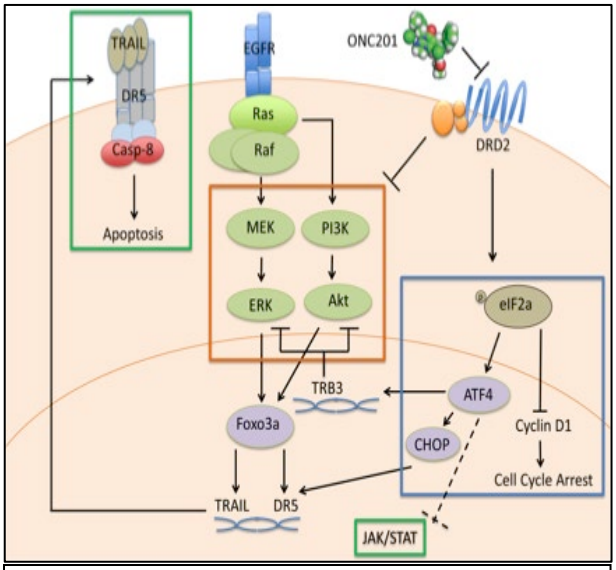



**Figure 7 Proposed model of ONC201 in tumor cells.**

Downstream of target engagement, ONC201 activates the integrated stress response (ISR), which is the same signaling pathway activated by ER stress-inducing compounds such as proteasome inhibitors (e.g. bortezomib). When the ISR is activated by ER stress-inducing compounds, the pathway is often referred to as the ER stress response. ONC201 causes an early-stage increase in the phosphorylation of eIF2-alpha at serine 51, which results in attenuation of protein translation and upregulation of the transcription factor ATF4 (**Fig. 7**). ATF4 upregulates CHOP, which is also a transcription factor that regulates several apoptosis-related genes such as the TRAIL-receptor DR5. ATF4 and CHOP upregulate expression of TRB3, which interacts directly with Akt to decrease its kinase activity. TRB3 also serves as a scaffold protein in the MAPK signaling pathway that can negatively regulate this pathway. Decreased levels of phospho-MEK, -ERK, and -Akt have been documented in response to ONC201. The decreased ERK and Akt kinase activity results in less phosphorylated Foxo3a, which is a transcription factor that regulates both the TRAIL and DR5 genes. Dephosphorylated Foxo3a undergoes nuclear translocation and activation in response to ONC201.

In summary, ONC201 inhibits DRD2 to cause downstream activation of ATF4, which causes induction of genes that lead to apoptosis. DRD2 antagonism also downregulates Akt and ERK activity to cooperatively induce complementary downstream apoptotic effects. ONC201 may not activate eIF2-alpha through PERK. This distinct mechanism may explain the lack of cross-resistance between ONC201 and other ER stress-inducing agents such as bortezomib. In addition, ONC201 has enhanced antitumor efficacy in combination with bortezomib that may be explained by engaging parallel stimuli that lead to an enhanced activation of the ISR in tumor cells.

ONC201 has been reported to decrease the phosphorylated active forms of the oncogenic kinases Akt, MEK, and ERK. The decreased phosphorylation of Akt and ERK causes decreased kinase activity, leading to dephosphorylation of its

substrates that include the mutual substrate Foxo3a[27]. ONC201-induced effects on these signaling pathways have been demonstrated in several tumor types in vitro with diverse genetic mutations in p53, KRAS, PTEN, and others**.** Targeting the Ras signaling pathway, which includes two arms ending at the effector kinases Akt and ERK, has been an unattainable therapeutic goal for decades[28]. Ras and its upstream activating receptors such as EGFR are very commonly activated in human cancer through mutations, amplification, or other mechanisms. This critical signaling pathway transduces stimulus signals from the extracellular environment into the nucleus to regulate genes that drive survival and proliferation. While the field widely accepts the enormous impact that inhibiting Ras would have in oncology, directly targeting Ras in tumors has not been performed successfully in the clinic. The challenge underlying this absence lies in the fact that Ras is a GTPase rather than a routinely drugged class of proteins such as a kinase. Nevertheless, targeting effector kinases downstream of Ras have been vigorously pursued in recent years as a chemically viable strategy by combining small molecule PI3K/Akt inhibitors with MEK/ERK inhibitors. While the dual inhibition of these pathways is widely reported to be synergistic it is plagued by toxicity and other limitations[29-31]. This combinatorial approach has several efficacy-limiting shortcomings that include toxicity [32] as these kinases are important for several physiological processes, compounding toxicity, drug-drug interactions, and the need for synchronous delivery to tumors.

In contrast to Akt and MEK inhibitors, ONC201 inactivates Akt and ERK indirectly in tumor cells while these kinases are uninhibited in normal cells. The lack of dual inhibition in normal cells means that ONC201 does not induce death of normal cell , allowing ONC201 to be safe at efficacious doses in cancer models in vitro and in vivo[26]. The inhibition of Akt and ERK in cancer cells is sustained following drug removal, maintained in the face of upstream mutations (e.g. KRAS), and is independent of upstream ligand stimulation (e.g. EGF). Furthermore, the ability of ONC201 to inhibit these two kinases as a single molecule results in concomitant dual inactivation that yields synergistic efficacy and also eliminates complications with combination therapy such as compounding toxicity and drug-drug interactions.

Recent gene expression profiling studies in solid and liquid tumor cell lines revealed transcriptome changes consistent with induction of the ER stress response.
Subsequent experiments validated that ONC201 activated the pro-apoptotic arm of ER stress in cancer cells, which is also activated by proteasome inhibitors. CHOP is a pro-apoptotic transcription that is induced as a critical effector of the maladaptive apoptotic ER stress response. Robust induction of CHOP expression in response to ONC201 treatment has been observed in multiple models in a response- and time-dependent manner. ER stress may be linked to prior observations related to Akt and ERK signaling in solid tumor cells with ONC201 treatment, as previously reported with ER stress-inducing compounds. Based on these findings, CHOP, pERK, pAkt, TRAIL, and DR5 should be evaluated for clinical utility as biomarkers in patients receiving ONC201 treatment.

### 1.5.3 **Pharmacokinetic studies in humans**

In a Phase I dose escalation clinical trial of ONC201 in advanced solid tumors, the pharmacokinetics of single agent ONC201 was determined by LC-MS-MS analysis of plasma collected in the first cycle of therapy within 21 days of drug administration (**Fig. 8**; **Table 1**). Trends of increasing exposure with dose were consistent with dose proportionality. Patients receiving 625mg ONC201 exhibited a mean half-life of 11.3 hours and achieved a Cmax of 3.6 ug/mL (~9.3 uM), which occurred at 1.8 hours following administration (Tmax). The mean volume of distribution was 369 L, consistent with a large distributive volume.

Mean AUC was 37.7 h.µg/mL and mean CL/F was 25.2 L/h. Generally, CL/F was observed to be variable but consistent across all dose groups. There were no apparent relationships between drug CL/F and patient sex and age. Noticeable, shallow trends were observed with patient weight and body surface area (BSA). An overall increase in CL/F was observed as weight and BSA increased. Although a slight upward trend was observed, there was no strong correlation between CL/F and CLCR.

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

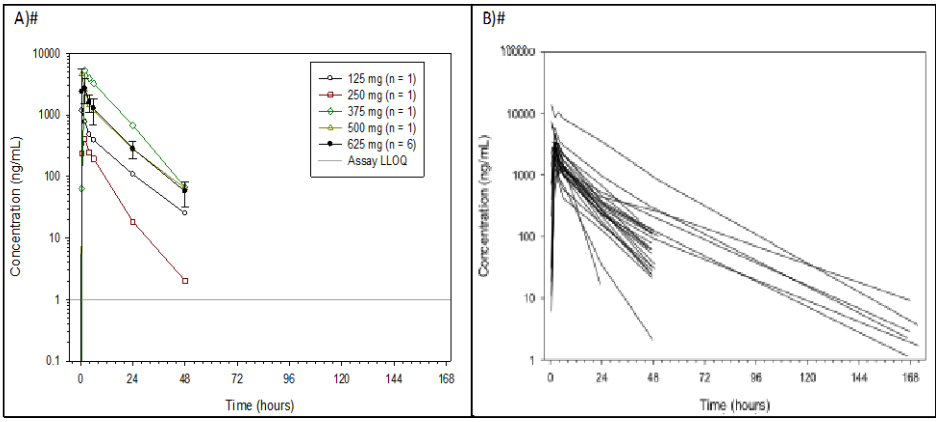



**Figure 8: Mean ONC201 plasma concentrations versus time following the first dose of ONC201.** Concentrations are shown as (A) A mean for each dose cohort, or (B) for individuals treated at 625 mg.

**Table 1 ONC201 pharmacokinetic parameters determined in patients receiving 625 mg ONC201 (n=24).**

| | $C_{max}$ | $T_{max}$ | $T_{lag}$ | $AUC_{last}$ | $\lambda_Z$ | $t_{1/2}$ | 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 |

In a Phase I/II clinical trial of ONC201 in adults with acute leukemias or high-risk myelodysplastic syndromes (NCT02392572), the pharmacokinetics of single agent ONC201 administered once every one or three weeks was determined by LC-MS-MS analysis of plasma collected in the first cycle of therapy within 21 days of drug administration. Oral doses of ONC201 were given at 125, 250, 375, 500 and 625mg, twice each week on two consecutive days (e.g. Monday and Tuesday of each week). This dosing schedule maintained systemic concentrations that exceeded 1,000ng/mL therapeutic thresholds of ONC201 for >72 hours in patients who received 375mg or 625mg. In contrast, exposure with weekly dosing generally maintained >1,000 ng/mL concentrations for <24 hours (Figure below). In vitro studies indicate that maximum antiproliferative and pro-apoptotic effects of ONC201 can require continuous incubation for at least 48 hours in some cancer cell lines.

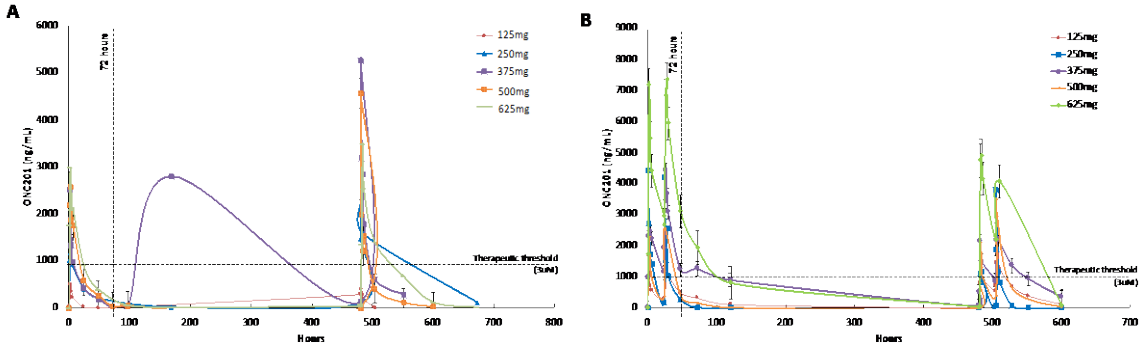



**Figure 9.** Plasma concentrations of ONC201 administered (A) once per week or (B) twice per week on two consecutive days to adults with relapsed/refractory acute leukemias or high-risk myelodysplastic syndromes. Hour 0 is the baseline sampled before the first dose on ONC201. Error bars reflect SEM of samples from patients enrolled to receive the same dose. **Based on this, the proposed dosing schedule of ONC 201 is 675mg twice weekly on two consecutive days.**

### 1.5.4 Clinical Studies

The clinical safety of ONC201 has been evaluated in a phase I clinical trial. The design was an open-label, dose-escalation phase I trial of mono-agent ONC201 in patients with advanced, refractory tumors who had exhausted or refused standard treatment options for their respective indications. The primary objective of this study was to determine the recommended phase II dose (RP2D) of ONC201 administered orally in

patients with advanced cancers, as well as to evaluate the safety and tolerability of the drug. Secondary objectives included pharmacokinetics and pharmacodynamics evaluation of ONC201 and preliminary assessment of anti-tumor efficacy.

An accelerated dose escalation design was employed to reduce the number of patients treated at potentially sub-therapeutic dose and to accelerate the determination of the recommended phase II dose. Ten evaluable patients (aged 47-80 years) received oral ONC201 once every 3 weeks at five dose levels ranging from 125 to 625 mg. The study design included only one patient per cohort until any patient experiences a grade 2 adverse event during the first cycle of treatment, defined as 21 days. Five dose levels (125 mg, 250 mg, 375 mg, 500 mg, 625 mg) were selected for the study. Enrollment at each subsequent dose level required that all patients enrolled at the prior dose level completed Cycle 1 dosing and were evaluated 21 days later to assess safety.

On average, patients received 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 metastasis with debilitating pain in the clavicle experienced relief from his clavicular pain. Patient #6, a 69-year-old patient with prostate adenocarcinoma, has received 7 doses of ONC201 and has stable disease. Patient #8, a 71-year old colon cancer patient had stable disease for at least 12 weeks with 4 doses of ONC201.

A 47-year-old male with appendiceal cancer (patient #2) had CA27.29 tumor biomarker of 30 units that was in the abnormal range, which decreased to 20 units (normal range) after 4 doses of ONC201. Given the heterogeneity of the tumor types in the enrolled patients, no widely used biomarker was available to uniformly assay all patient samples. Since most solid tumors express cytokeratin-18, the serum M30 assay was selected to detect a caspase-cleaved form of cytokeratin-18 that occurs during apoptosis. Clinical studies have demonstrated the M30 assay to be predictive of clinical response [33] in solid tumors. Induction of the M30 assay for apoptosis was noted in 67% of patients treated at the RP2D with a range of 1.25- to 4-fold increase.

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

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

A clinical trial is currently being conducted at the MD Anderson Cancer Center investigating the safety of ONC201 in patients with acute leukemias and myelodysplastic syndrome (study #2014-0731; NCT02392572). Thus far, 9 patients have been enrolled in this study using 2 administration schedules – once every 3 weeks and once every week. 6 patients were dosed at once every 3 weeks schedule at various dose escalation cohorts (125mg, 250mg, 365mg, 500mg, 625mg) and 3 patients were dosed on weekly cohorts (125mg, 250mg, 375mg). There were reported instances of febrile neutropenia, lung infection (pneumonia), gastrointestinal disorders and abdominal pain. None of these adverse events were attributed as drug-related by the investigator.

Study #2014-0632 (NCT02420795) being conducted at the MD Anderson Cancer center, is a 3+3 design dose-escalation design to determine the safety of ONC201 in patients with relapsed/refractory Non-Hodgkin's Lymphoma (NHL). Thus far, 3 patients have been enrolled at 125 mg and 1 patient at 250 mg dosed once every 3 weeks. In addition, 1 patient has also been enrolled at the weekly schedule and has received twelve 125mg doses. No drug-related adverse events have been reported.

Study #PH-077 (NCT02609230) is a Phase I dose-escalation study of ONC201 in patients with solid tumors and multiple myeloma, being conducted at Fox Chase Cancer Center. Thus far, 6 patients have received ONC201 125mg once every 3 weeks. Patient 1 experienced an SAE that was initially assessed as possibly drug related (progressed from Grade 2 fatigue at baseline to Grade 3 fatigue). The patient had brain metastases at baseline and rapid progression of underlying disease and associated symptoms within 2 weeks of initiating ONC201 treatment. The SAE attribution that triggered the initial report is under reassessment based on the evidence of progressive underlying disease.

Study #15-318 (NCT02525692) is a Phase II study of ONC201 in patients with recurrent glioblastoma, being conducted at Massachusetts General Hospital and Dana

Farber Cancer Institute. 17 patients have been treated to date at 625mg ONC201 once every three weeks. One patient had a possibly drug-related incident of abnormal neutrophil count that was quickly resolved and classified as not-serious and the same patient had a mild allergic reaction after 6 doses. In this study, another patient had a PR with a 82% decrease in tumor volume after 8 doses of drug and is still on therapy, while another patient remains disease-free for more than 32 weeks.

### 1.6 Circulating Tumor Cells (CTCs) to assess TRAIL receptor expression

CTCs will be isolated by a novel microfluidics CTC platform (VERSA Chip) that integrates CTC capture (>90% efficiency) with quantitative immunofluorescence and nucleic acid extraction/analysis[34-39]. CTCs will be captured using multiple antibodies (EpCAM, cell surface vimentin, MUC1, and CD133) determined by analysis of CTCs isolated in preclinical studies. Captured CTCs will be analyzed by quantitative immunofluorescence (TRAIL, TRAIL-R1 and TRAIL-R2) followed by RT-PCR analysis of mRNA levels of these targets using the VERSA Chip[37, 38].

CTCs will be drawn and analyzed if funding is secured.

### 1.7 Study rationale

We hypothesize that ONC201 with an intermittent MR-diet will be effective in patients with metastatic TNBC. Expression of TRAIL receptor will be assessed in CTCs.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1 Primary Objective:

2.1.1 To determine objective response rate (ORR) to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.

### 2.2 Secondary Objectives:

2.2.1 To determine progression-free survival (PFS) to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.

2.2.2 To determine clinical benefit rate (complete and partial response plus stable disease) (CBR) at 4 months to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.

2.2.3 To determine overall survival (OS) to ONC201 with a methionine-restricted diet in patients with metastatic TNBC.

2.2.4 To determine the safety of adding a methionine-restricted diet to ONC201 in patients with metastatic TNBC

2.2.4 To assess metabolic indices in patients with metastatic TNBC treated with ONC201 and a methionine-restricted diet.

2.2.5 To assess the expression of TRAIL receptor in CTCs prior, during and upon progression in patients with metastatic TNBC treated with ONC201 with a methionine-restricted diet.

**2.3 Exploratory Objective:**

2.3.1 To determine time to development of brain metastases or worsening of brain metastases in patients with metastatic TNBC treated with ONC201 with a methionine-restricted diet.

## 3. ELIGIBILITY CRITERIA

### 3.1 Inclusion criteria

_____ 3.1.1 Metastatic or unresectable TNBC (ER<10%, PR< 10% and HER2 negative either by IHC or in situ hybridization method by ASCO-CAP guidelines). For patients with a previous tumor sample with positive ER, PR and/or HER2 results, if the most recent biopsy meets study criteria, they will be eligible

_____ 3.1.2 Measurable disease by RECIST 1.1. within 28 days prior to registration.

_____ 3.1.3 Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately

_____ 3.1.4 Females 18-74 years of age at the time of consent. Men are not eligible to participate.

_____ 3.1.5 Any number of prior lines of systemic therapy for metastatic disease.

_____ 3.1.6 ECOG PS of 0 or 1

_____ 3.1.7 Prior cancer treatment, including radiotherapy, must be completed at least 14 days prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen to ≤ grade 1 or to baseline prior to initiation of that therapy. Grade 2 or higher exceptions include alopecia, up to grade 2 neuropathy or lymphopenia,and other grade 2 AEs or lab values not constituting a safety risk in the opinion of the treating physician. This criterion does not apply to lab tests outlined in criteria 3.1.10.

_____ 3.1.8 No active CNS metastatic disease; subjects with prior definitive treatment of their CNS disease by surgical resection, SBRT or WBRT >28 days ago will be eligible if asymptomatic and off systemic steroids.

_____ 3.1.9 Life expectancy of greater than 12 weeks.

_____ 3.1.10 Normal organ and marrow function as defined per protocol definitions.

a. ANC $\geq$ 1.5 x $10^3/\mu L$
b. Platelet count $\geq$ 100 x $10^3/\mu L$
c. Hemoglobin $\geq$ 9 g/dL
d. Total bilirubin $\leq$ 1.5 x ULN
e. Transaminases AST/SGOT and ALT/SGPT ≤ 2.5 x ULN. If patient has liver metastases, ≤ 5x ULN.
f. Creatinine $\leq$ ULN (institutional normal)

_____ 3.1.11 Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

_____ 3.1.12 Females of childbearing potential must be willing to abstain from heterosexual activity or must agree to use adequate contraception (hormonal or barrier method) for the duration of study participation and for 90 days after discontinuation of study treatment.

_____ 3.1.13 Ability of the subject to understand and comply with study procedures for the entire length of the study.

_____ 3.1.14 Able to swallow ONC201

_____ 3.1.15 Be willing to discontinue vitamin and mineral supplements for the duration of the study if randomized to receive the methionine restricted diet.

**3.2 Exclusion criteria**

_____ 3.2.1 No prior therapy with TRAIL receptor agonists

_____ 3.2.2 Active infection requiring systemic therapy. Patients with a known history of HIV must have a CD4 count ≥ the institutional lower limit of normal within 28 days prior to registration. Patients with HIV must also be on a stable anti-retroviral regimen for ≥ 28 days before registration.

_____ 3.2.3 Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

_____ 3.2.4 Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least three years.

_____ 3.2.5 Treatment with any investigational drug agent ≤ 14 days prior to registration or within 5 half-lives of that investigational product, whichever is longer.

_____ 3.2.6 Subject who has had major surgery ≤ 14 days prior to registration or has not recovered from major side effects of the surgery (tumor biopsy is not considered as major surgery).

_____ 3.2.7 Known hypersensitivity to any of the excipients of ONC201.

_____ 3.2.8 Any impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

_____ 3.2.9 Any concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate subject participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).

_____ 3.2.10 Patients who follow a vegan or vegetarian diet

_____ _____
Investigator Signature Date

_____ _____
Coordinator Signature Date

## 4. REGISTRATION PROCEDURES

### 4.1 Patient Registration

Each subject enrolled in the study is to be registered into the UWCCC OnCore Database prior to starting protocol treatment. Research personnel at WON sites who enter data into OnCore must have completed human subjects training and Health Insurance Portability and Accountability Act (HIPAA) training. WON site research personnel receive training from UWCCC staff on how to enter subject data into OnCore.

At the time of registration, the following will be required and verified by UWCCC:

- Copy of required laboratory tests
- Signed subject consent form
- HIPAA authorization form
- *Eligibility Screening Worksheet*

To complete the registration process, UWCCC staff will:

- assign a subject study number
- register the subject on the study
- fax or e-mail the subject study number to the participating site

### 4.2 General Guidelines

Following registration, subject must have cycle 1 day 1 within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy or MR diet following registration, the subject may be replaced.

## 5. TREATMENT PLAN

### 5.1 Overview of treatment plan

This is a phase 2 trial in which subjects will receive ONC201 with a MR diet.

### 5.2 ONC201 administration

The study drug, ONC201, will be supplied in capsule form for oral dosing. ONC201 625 mg (5 tablets of 125 mg each) will be given by mouth on Days 3 and 4 of each week for each cycle (administered on days 3,4, 10,11 and 17,18). Treatment will be administered primarily on an outpatient basis, but can be administered as an inpatient. A cycle is equal to 21 days.

Subjects should take the dose of ONC201 specified by their physician 2 hours prior or 2 hours following food or a meal. If the subject vomits after taking ONC201, they should not retake the dose. Missed doses will not be made up, if more than 1 day pass from the intended day of administration.

ONC201 should be taken with a glass of water and consumed over as short a time as possible. Subjects should swallow the capsules as a whole and not chew them. Do not crush or empty the capsule. If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted as an adverse event.

### 5.3 Methionine-restricted diet

Under the supervision of a registered dietitian (either at the site or from the coordinating site) and the site investigator, subjects will receive an individualized dietary prescription that incorporates a methionine-free amino acid-modified

medical food (Hominex-2, Abbott Nutrition) supplemented with low-methionine foods (**Table 2**). Hominex-2 contains a mixture of L-amino acids but lacks methionine. Subjects will be instructed by the dietician in the preparation of Hominex-2 shakes to deliver 100% of daily protein requirements (0.8 g/kg/day) and 75% of the caloric requirements. The remaining calories will be met with low-methionine foods, including fruits, vegetables, grains (*e.g*., specified cereal and bread), margarine and cooking oils. Subjects will be provided with a list of foods that are low in methionine. Calories will not be restricted. Subjects will be encouraged to follow their usual level of physical activity and instructed to maintain a daily diet and exercise diary that will be reviewed by the dietitian. Subjects will take the MR diet days 1 through 5 of each week (defined as a 7-day period) while taking the ONC201 Subjects may resume a general diet on days 6 and 7 each week. Phase I and phase II trials of a methionine-free diet alone or in combination with chemotherapy in subjects with metastatic or recurrent solid tumors have confirmed the safety and tolerability of methionine deprivation (up to 39 weeks)[24, 25].

A 24-hour dietary recall exercise [40] will be completed by a dietician prior to starting the methionine restricted diet during cycle 1. The recall and food diaries will be analyzed using Food Processor® Nutrition and Fitness Software, ESHA Research, Salem, OR, USA. Food intake will be entered in and a report detailing the nutritional components of the food taken will be generated and provided back to the dietician. Gender, age, height and weight will be entered for use with the analysis of the diet taken. This dietary analysis will not be provided to the subjects.

**Table 2: Methionine-restricted diet shakes**

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Premedications; Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Methionine-free amino acid-modified medical food | None | shakes | Oral | Per dietician recommendation | Days 1 through 5* of every 7-day period. Cycle = 21 days |

*Subjects should follow the methionine restricted diet for days 1-5 of every 7-day period. However, 1 day of methionine restriction may be skipped in this 5-day restriction period if needed to allow flexibility around holidays, vacations, etc. The 4-5 days of the diet during each 7-day period must be consecutive. The diet must be

followed for a minimum of 24 hours prior to the collection of CTCs and for a minimum of 24 hours prior to dosing with ONC201.

The subject will be requested to maintain a medication diary of each dose of medication. The medication diary (one for ONC201 and for the shakes) and the diet/exercise diary will be returned to clinic staff at the end of each cycle of therapy. It will not be a deviation if the subject isn't able to complete the diet/exercise diary. Subjects will meet with the dietician on day 1 of cycles 1 and 2 to review the diet/exercise diary. Additionally, the dietician will contact the subject during the initial week of cycle 1 to assess tolerance of the diet and to address questions the subjects may have. Subjects will be able to contact the dietician during normal business hours to discuss dietary questions or concerns related to the study.

Recipes for the methionine restricted shakes will be developed to fit the needs of individual subjects (taste preferences, energy needs, etc.).

## 5.4 Study drug compliance and accountability

Compliance will be assessed by the investigator and/or study personnel at each subject visit at each participating site. Drug diaries will be used by subjects to record study medication taken and number of shakes taken. A drug accountability log at each respective site will be used to track the receipt and dispensing of ONC201.

## 5.5 Concomitant medications

### 5.5.1 Allowed concomitant medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal medications are allowed. In general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited below.

The subject must be told to notify their respective participating investigational site staff about any new medications she takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies section of the subject record.

<u>Bisphosphonates and Denosumab:</u>
Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for subjects with bone metastases.

<u>Hematopoietic growth factors:</u>
Hematopoietic growth factors may be used according to ASCO guidelines.

### 5.5.2 Prohibited concomitant medications

To date, no prohibited concomitant medications have been identified.

## 5.6 Supportive care Guidelines

Supportive measures including analgesics, blood transfusions, anti-microbials and hematopoietic colony stimulating factors for treatment of cytopenias are permitted.

**Nausea/vomiting:**

Subjects with treatment-related nausea should be treated initially with a phenothiazine (prochlorperazine – 10 mg every 8 hours orally as needed). If this is inadequate, a benzodiazepine or ondansetron 4-8 mg orally should be added until acute nausea is controlled or toxicity is limiting.

After acute nausea has resolved, consideration should be given to initiation of prophylactic antiemetic therapy. If nausea recurs despite reasonable medical intervention (as outlined above), dose reduction will be needed as described.

**Diarrhea:**

Diarrhea should be managed with loperamide: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea is controlled (maximum = 16 mg loperamide per day).

**Neutropenia and Neutropenic fever and other cytopenias:**

Subjects with neutropenic fever or infection should be evaluated promptly and treated with IV antibiotic therapy or therapeutic colony-stimulating factors as appropriate following the ASCO guidelines. Packed red blood cell and platelet transfusion should be administered as clinically indicated.

# 6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (v5.0) will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar.

## 6.1 Adjustments to Methionine-Restricted Diet

The dietician may modify the volume and concentration of shakes to increase tolerability.

Best supportive care should be used for side effects attributable to the methionine restricted diet/medical food.

Subjects who discontinue the methionine restricted diet may continue ONC201.

**Table 3: Dose adjustment rules for Adverse Events (in addition to Table 5 below)**

| **CTCAE Grade** | **Management for the methionine-restricted diet** |
|---|---|
| **Weight loss** | |
| Grade 2 or higher | Methionine restricted diet must be discontinued. |
| **Homocysteine levels** (to be captured as: Metabolism and Nutrition disorders – other, specify) | |
| Grade 2 or higher | Methionine restricted diet must be discontinued |

Normal homocysteine levels are 5-15 micro mol/L.
For purposes of this study homocysteine levels will graded per the table below:

**Table 4**:

| | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Homocysteine Level | ≥15 - <30 micro mol/L | ≥ 30 - < 100 micro mol/L | ≥ 100 micro mol/L |

## 6.2 ONC201 Dose Adjustments

The descriptions and grading scales found in the revised NCI CTCAE v5.0 will be utilized for dose delays and dose modifications

Criteria for disrupting treatment, dose modification, or discontinuation are listed in **Table 5**.

For subjects who do not tolerate the dosing schedule, dose adjustments are permitted in order to allow the subject to continue the study treatment.

Below are dose modifications (**Table 5**) for adverse events that are at least possibly, probably or definitely attributable to study drug, including: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. If a patient experiences other adverse

events, or several adverse events and there are conflicting recommendations based on grade, the investigator will use the recommended dose adjustment that reduces the dose. Dose modifications will be made based on an adverse event that occurs any time during a cycle.

**Table 5: Dose adjustment rules for Adverse Events (AEs),** including nausea, diarrhea, neutropenia, thrombocytopenia, and other AEs. Alopecia does not require dose adjustments. Lymphopenia does not require dose adjustment unless clinically significant per treating physician.

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

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

### 6.3 Protocol therapy discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Documented disease progression
- Discontinue methionine restricted diet for weight loss grade 2 or higher
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be

contacted for further scheduled study assessments. The outcome of that discussion should be documented in the medical records.

- A female subject becomes pregnant
- If protocol therapy is interrupted for >21 days.

Subjects will be removed from protocol therapy, and the site investigator notified, when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the eCRF in OnCore.

Subjects who discontinue protocol therapy will be followed every 3 months for 2 years after the end of treatment visit. Survival status and anti-cancer therapy (to include only first cancer directed therapy after study) will be collected from review of medical records or via telephone follow up.

If subjects discontinue study treatment prior to disease progression, scans during follow-up will be completed per standard of care, but RECIST measurements must be completed until disease progression or start of new anti-cancer therapy.

### 6.4 Evaluable subject

**Evaluable for response:** Any subject who receives at least 80% of ONC201 doses during the first two cycles of treatment (i.e., at least 9 doses of ONC201) and have at least one disease re-evaluation will be evaluable for response. Dose reductions will not be included in this 80%, just number total doses taken will be included.

**Evaluable for toxicity:** Any subject who receives at least one dose of treatment on this protocol should be evaluable for toxicity. Safety will be assessed by NCI CTCAE v5.0.

### 6.5 Protocol discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible until the date of withdrawal. The treating investigator should contact the subject or a responsible relative by telephone to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

### 6.6 Criteria for Early Trial Termination

Early trial termination will occur if any of the following are met:

a. Incidence or severity of adverse drug reactions in this or other studies using this drug that indicates a potential health hazard to subjects.
b. Plans to modify or discontinue the study drug (ONC201), such that the original study drug is no longer provided by the sponsor.

c. Financial support of the study is withdrawn such that protocol activities can no longer be conducted.
d. If enrollment or subject withdrawal will impact the ability of the study to meet the stated objectives.
e. UWCCC Data Safety Monitoring Committee recommendation based on review of required study documents (outlined in section 12).

## 7. STUDY CALENDARS AND EVALUATIONS

| Cycle = 21 days | Screening | Cycle 1 | Cycle 2 | Odd # cycles Begin at Cycle 3 | Even # cycles Begin at Cycle 4 | End of Treatment | Long-term Follow-up |
|---|---|---|---|---|---|---|---|
| | -28 days | Day 1 +/- 2 days | Day 1 +/- 2 days | Day 1 +/- 2 days | Day 1 +/- 2 days | 35 days from last dose of study treatment +/- 5 days | Every 3 months (+/- 7 days) for 2 years from EOT |
| Informed consent | X | | | | | | |
| Medical history | X | | | | | | |
| Diagnosis and staging | X | | | | | | |
| Physical Exam | X | X[13] | X | X | X | X | |
| Vital signs, wt, waist circumference[8], ECOG performance status | X | X[13] | X | X | X | X | |
| AEs & concomitant medications, drug diary review[7] | X | X | X | X | X | X | |
| | LABORATORY ASSESSMENTS | | | | | | |
| CBC with differential (minimum to include: Hgb, WBC, Plt, ANC) | X | X[13] | X | X | X | X | |
| CMP[9] | X | X[13] | X | X | X | X | |
| Blood for metabolic indices[1] | | X | X | | X | X | |
| Homocysteine/ cysteine[11] | | X | | X | | X | |

| Cycle = 21 days | Screening | Cycle 1 | Cycle 2 | Odd # cycles Begin at Cycle 3 | Even # cycles Begin at Cycle 4 | End of Treatment | Long-term Follow-up |
|---|---|---|---|---|---|---|---|
| | -28 days | Day 1 +/- 2 days | Day 1 +/- 2 days | Day 1 +/- 2 days | Day 1 +/- 2 days | 35 days from last dose of study treatment +/- 5 days | Every 3 months (+/- 7 days) for 2 years from EOT |
| Pregnancy test (serum)[6] | - 7 days | X[6] | | | | | |
| Diet/Exercise Diary | | X | X | X | X | | |
| 24 Hour Dietary Recall Form | | X | | | | | |
| | DISEASE ASSESSMENTS | | | | | | |
| CT chest, CT or MRI of abdomen and pelvis[10] | X | | | | X[10] | | X |
| MRI brain | X[3] | | | | | | |
| Bone scan | X[3] | | | | X[3] | | |
| | TREATMENT EXPOSURE | | | | | | |
| ONC201 | | Days 3 and 4, weekly | Days 3 and 4, weekly | Days 3 and 4, weekly | Days 3 and 4, weekly | | |
| MR diet | | Days 1 -5 weekly | Days 1 - 5 weekly | Days 1 - 5 weekly | Days 1 - 5 weekly | | |
| | CORRELATIVE STUDIES (SPECIMEN COLLECTION) | | | | | | |
| Archival Tissue[12] | X | | | | | | |
| Circulating tumor cells | | X[5] | X[5] | | | X[5] | |
| Plasma methionine & methionine metabolites | | X[2] | X[2] | | X[2] | X[2] | |
| | FOLLOW-UP | | | | | | |
| Survival | | | | | | | X |

(1) Blood will be taken to assess metabolic indices at baseline, cycle 2 day 5, then day 5 of every other cycle, and at end of treatment. Indices are fasting: glucose, insulin, IGF-1, and leptin levels. If necessary, these labs may be drawn as early as day 2, but prefer to be as close to day 5 as possible without going over.
(2) Blood will be taken to assess plasma methionine levels at baseline, cycle 2 day 5, then day 5 of every other cycle, and at end of treatment. Subjects must be fasting. If necessary, these labs may be drawn as early as day 2, but prefer to be as close to day 5 as possible without going over.
(3) If clinically indicated.
(4) Optional biopsy prior to study entry.
(5) Blood for circulating tumor cells will be taken at baseline, day 5 of cycle 2, and at end of treatment. If necessary, these labs may be drawn as early as day 2, but prefer to be as close to day 5 as possible without going over.
(6) For women of childbearing potential. To be completed within 7 days of randomization. Must be repeated at cycle 1 day 1 if not completed in previous 7 days.
(7) Subjects whose treatment is interrupted or permanently discontinued due to an adverse event (including lab values) should be followed per section 11.1.1.
(8) Waist circumference, optional if not possible due to site limitations. Not required at screening.
(9) CMP to include sodium, potassium, chloride, carbon dioxide, glucose, BUN, creatinine, calcium, albumin, total protein, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin.
(10) CT chest with or without contrast and CT with contrast or MRI of Abdomen/Pelvis to be completed during screening and ≤ 7 days prior to every third cycle starting at cycle four (approximately every 9 weeks; e.g. cycles 4, 7, 10, etc.). If subjects discontinue study treatment prior to disease progression, scans during follow-up will be completed per standard of care, but RECIST measurements must be completed until disease progression or start of new anti-cancer therapy.
(11) Homocysteine/cysteine level at: baseline and every 3 cycles while on study (C1, C4, C7, etc.) and at end of treatment.
(12) One block or 10 unstained slides.
(13) labs/physical exam/ECOG PS does not need to be repeated if done within 7 days prior to C1D1

## 8. BIOSPECIMEN STUDIES AND PROCEDURES

### 8.1 Tumor tissue

Subjects will be consented for use of archived tissue for analysis. To determine the effects of dietary MR on tumor expression of TRAIL receptors, mRNA levels of TRAIL-R1 and TRAIL-R2 will be determined by real-time PCR. In addition, quantitative immunofluorescence of cell surface TRAIL-R1 and TRAIL-R2 expression in breast tumor cells identified by cytokeratin expression will be determined by automated quantitative analysis (AQUA) of digitally captured images. These studies will be performed in the UW Carbone Cancer Center Translational Research Initiatives in

Pathology (TRIP) Lab under the supervision of our co-investigator Dr. Andreas Friedl. We will also determine the effects of treatment on the expression of the cancer stem cell markers CD44 and CD24 by immunohistochemistry.

### 8.2 Circulating tumor cells (CTCs)

If funding is secured, CTCs will be enumerated and evaluated for TRAIL expression. We hypothesize that treatment with MR diet will increase the expression of TRAIL receptors on CTCs and reduce the number of CTCs.

**Time points:** CTCs will be collected at baseline, on day 5 of cycle 2, and at end of treatment. If the CTC sample is not collected at baseline, the remaining samples should not be collected. Missed CTC samples will not be considered a protocol deviation.

Please note that CTC samples must be shipped Monday –Thursdays only. Samples must be shipped to arrive at the Lang lab by Fridays by 12:00 p.m. CTC samples will be drawn only at those sites identified by the coordinating site as having adequate resources (shipping and funding) to provide the samples.

**Sample Requirements:**

Please refer to the Study Procedures Manual for sample collection, processing, labeling, and shipping instructions.

### 8.3 Plasma methionine and methionine metabolites

Blood will be collected after an overnight fast before dietary methionine restriction at baseline, cycle 2 day 5, then day 5 of every other cycle, and at end of treatment. Plasma will be stored at -80º C for analyses of methionine and its metabolites. Plasma concentrations of methionine and methionine metabolites [5'-methythioadenosine (MTA), homocysteine (Hcy), S-adenosylhomocysteine (SAH), and S-adenosylmethionine (SAM)] will be determined by high-throughput targeted LC-MS assay to measure methionine and these metabolites. Using these methods, we demonstrated that TNBC cells grown in 0% methionine have robust reductions in methionine levels and modest reductions in some methionine metabolites. Plasma methionine levels are predicted to serve as an index of dietary compliance.

Blood samples (one 6 mL heparinized green top tube per timepoint) will be drawn and processed at the CRU, stored in Professor Vincent Cryns' lab at -80º C, and sent in batches to the Laboratory of Professor Josh Coon in the UW Department of Chemistry. All samples provided will be identified by UWCCC study number, unique subject number and date and time sample was collected. Outside sites should refer to the Study Procedures Manual for collection, processing, labeling, and shipping instructions.

### 8.4 Confidentiality of biospecimens

Samples that are collected will be identified by the study number, the subject's study number assigned at the time of registration to the trial and the date and time of

sample collection. Any material issued to collaborating researchers will be anonymized and only identified by the subject's unique sequence number, study number, date of collection.

## 9. CRITERIA FOR DISEASE EVALUATION

The following sections describe the recommended method to track disease response for solid tumor trials as per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[41]

### 9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

**Malignant Lymph Nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

### 9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

**NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### 9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the

diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

### 9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 9.5 Evaluation of Target Lesions

**NOTE:** In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD) | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study |

### 9.6 Evaluation of Non-target Lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)<br><br>Note: If tumor markers are initially above the upper normal limit, they must normalize for a |

| | |
|---|---|
| | subject to be considered in complete clinical response. |
| Non-CR/ Non-PD | Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD) | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. |

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the investigator at the respective participating site should prevail in such circumstances, and the progression status should be confirmed at a later time by the UW investigator.

## 9.7 Evaluation of Best Overall Response

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/ Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD/ or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | Non-evaluable |
| PD | Any | Yes or No | PD |
| Any | PD* | Yes or No | PD |
| Any | Any | Yes | PD |
| *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. | | | |

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

**Confirmatory Measurement/Duration of Response**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4-6 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see below).

| **Overall Response First time point** | **Overall Response Subsequent time point** | **Best Overall Response** |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD/PD/PR* |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| NE | NE | NE |

* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

## 9.8 Definitions for Response Evaluation – RECIST 1.1

### 9.8.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

### 9.8.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

### 9.8.3 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

### 9.8.4 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

### 9.8.5 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

### 9.8.6 Progression-Free Survival
A measurement from the date of treatment initiation until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

### 9.8.7 Overall Survival
Overall survival is defined by the date of treatment initiation to date of death from any cause.

# 10. DRUG INFORMATION

## 10.1 ONC201

### 10.1.1 Drug Product Supply and Inventory
Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Availability: ONC201 is provided by Oncoceutics Inc.

Accountability: The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Destruction and Return: Unused supplies of the agent should be returned to the Sponsor within 60 days of the completion of the study. Unused supplies of the agent may also be destroyed on-site upon completion of the study, after accountability has been audited by the Sponsor or designated representative.

Dispensing:
ONC201 must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. ONC201 should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

### 10.1.2 **Pharmaceutical information**

The study drug ONC201 is provided as 125 mg free base (approximately 150 mg of dihydrochloride), with or without microcrystalline cellulose, filled into hydroxypropyl methylcellulose (HPMC) capsule shells. Alternative strengths may be manufactured.

The ONC201 drug product capsules are intended for oral administration. The product is stored in a multi-dose container. The capsules are packaged in high-density polyethylene (HDPE) white opaque bottles, closed with an induction seal and capped with a white ribbed SecuRx® polypropylene (PPE) cap.

The capsules are to be stored in the original closed container at room temperature (15 to 30°C).

The study drug bottle label bears the following information. If alternative strengths are manufactured, the dosage on the label will be inserted in place of '125 mg'.

**ONC201 Capsules, 125 mg**

**For Oral Use Only**

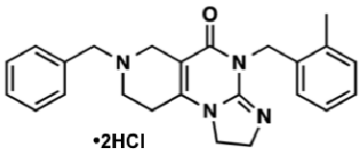
**Caution: New Drug--Limited by Federal (or United States) law to investigational use.**

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

**Sponsor:** Oncoceutics, Inc.

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

## Drug Substance Description

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

**Form:** ONC201 will be provided as hydroxypropyl methylcellulose (HPMC) capsules filled with the active ingredient (ONC201 dihydrochloride), intended for oral administration. The ONC201•2HCl drug substance is a white to off-white solid. The drug product will be packaged as 25 capsules per bottle. The capsules are filled into 30cc high-density polyethylene (HDPE) white opaque bottles with induction seal and 28mm white ribbed SecuRx polypropylene (PPE) cap.

Storage and Stability: Based on the current stability data at 40°C/75%RH room temperature (25°C/60%RH) will be used for the drug product storage. Drug product stability studies found no change after 1 month at 40°C/75%RH when stored with or without desiccant. Similarly no changes have been observed when stored a room temperature for 1 year. Clinical trial batches will be produced without desiccant. No shelf-life has been established for this product at this point. However, representative

clinical trial batches have been placed on stability. Any batches that are out of specifications will be removed from the trial.

For the ONC201 drug substance, stability results show little to no change in assay, impurities or appearance. The only changes observed under the accelerated conditions (40°C/75%RH) where a slight increase in moisture content was observed, from 1.2% at time 0, to 6.5% at 2 months, and to 6.2% at 3 months. The moisture content plateaued at approximately the monohydrate. The increase in moisture content did not result in increased impurity levels or decreased potency. These results suggest robust stability of the drug substance when stored at room temperature and accelerated conditions.

### 10.2 Hominex-2 shakes

Subjects will receive an individualized dietary prescription that incorporates a methionine-free amino acid-modified medical food (Hominex-2, Abbott Nutrition) supplemented with low-methionine foods. Hominex-2 is an amino acid modified medical food that contains a mixture of L-amino acids but lacks methionine. It is used to provide nutritional support for individuals with vitamin B6-nonresponsive homocystinuria or hypermethioninemia. Additional information is available at: http://abbottnutrition.com/brands/products/hominex-2

## 11. ADVERSE EVENTS

### 11.1 Definitions

#### 11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. AEs will be graded using the NCI CTCAE v5. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

All subjects who discontinue study treatment, including those who refuse to return for a final visit, should be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) within 30 days after the last dose of study drugs. Subjects whose treatment is interrupted or permanently discontinued due to an adverse event should be followed at least weekly for four weeks via telephone or in-person visit per physician discretion. Subsequently they should be followed at a minimum of 4-week intervals until resolution or stabilization of the event. If subject discontinues study treatment due to an abnormal lab value, appropriate laboratory

testing should be repeated per physician discretion (minimum ≤ once per week) until resolution to ≤ grade 1 or the treating physician determines the value is not expected to improve.

### 11.1.2 **Serious Adverse Event (SAE)**

An SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events. Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (i.e. to perform study related assessments), elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent, social reasons and respite care in the absence of any deterioration in the subject's general condition or treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

### 11.1.3 **Unexpected Adverse Event**

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### 11.1.4 **Relatedness**

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

| | |
|---|---|
| **Unrelated** | The Adverse Event is ***not related*** to the drug(s) |
| **Unlikely** | The Adverse Event is ***doubtfully related*** to the drug(s) |
| **Possible** | The Adverse Event ***may be related*** to the drug(s) |
| **Probable** | The Adverse Event is ***likely related*** to the drug(s) |
| **Definite** | The Adverse Event is ***clearly related*** to the drug(s) |

### 11.2 Procedures for Recording and Reporting Adverse Events

#### 11.2.1 **Adverse Events**

- AEs will be recorded from time of informed consent until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record, AE log in the subject research chart, and on the appropriate study specific eCRF form within OnCore.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- All WON sites should follow the AE reporting procedures outlined in the WON Operations Manual in addition to following the non-UW specific procedures outlined above

#### 11.2.2 **Reporting of Pregnancy:**

- Pregnancy will be reported from time of first study drug until 30 days after discontinuation of either study drug(s).
- Pregnancy will be reported to UW as an SAE **within 1 business day** of discovery of the event.
- Pregnancy follow-up will be reported to UW as follow-up to the initial SAE.

The pregnancy will be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Each local site investigator is responsible for informing the IRB and/or other local regulatory bodies of the event as per local requirements.

### 11.2.3 **Serious Adverse Events (SAEs)**

#### 11.2.3.1 Site Requirements for Reporting SAEs

- SAEs will be reported from time of on-study until 30 days after discontinuation of either study drug(s).
- Any SAEs experienced after this 30-day period will only be reported if the investigator suspects the event is at least possibly related to the study treatment.
- SAEs will be reported to Oncoceutics within 24 hours of discovery of the event. Reporting to the UWCCC will occur per the timelines listed in table 5.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs, regardless of relation to study drug, will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Please see section 12.4 for SAE reporting requirements.

## 12. DATA AND SAFETY MONITORING PLAN

### 12.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Reviews reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.

- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

## 12.2 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for this trial are as follows:

### 12.2.1 Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. These discussions may include the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

## 12.3 Review and Oversight Requirements

### 12.3.1 Serious Adverse Event – Reported within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 5 calendar days, all available subsequent SAE documentation must be submitted electronically along with a 24-hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC. If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators. For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

### 12.3.2 **Serious Adverse Event – Reported within 10 Days**

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the DSMC Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

### 12.3.3 **Sponsor-Investigator Responsibilities for SAE Review**

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAE with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 7 calendar days.

Refer to Section 12.5 for UWCCC PI instructions for reporting to the FDA.

### 12.3.4 **Study Progress Review**

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, toxicities and

responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

### 12.4 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 5 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee (DSMC) Chair. Serious adverse events must also be reported to the UW IRB per their guidance (https://kb.wisc.edu/hsirbs/18324#UP), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the SAE in question by using the following table. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at a WON Site.

**Table 5. Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1,2]**

| **FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)** |
|---|
| **NOTE:** Investigators **MUST** immediately report to the University of Wisconsin Carbone Cancer Center and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).<br>An adverse event is considered serious if it results in ANY of the following outcomes:<br>1) Death. |

2) A life-threatening adverse event (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the UWCCC within the timeframes detailed in the table below:

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes |
|---|---|---|
| **Resulting in hospitalization ≥ 24 hrs** | 10 Calendar Days | 24 Hour; 5 Calendar Days |
| **Not resulting in Hospitalization ≥ 24 hrs** | Not required | |

**Expedited AE reporting timelines are defined as:**

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

### 12.4.1 **SAE Requiring 24 hour Reporting Occurs at UWCCC:**

#### 12.4.1.1 Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=54655) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports**. A follow-up report is required to be submitted within 5 calendar days of the initial [24] hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a. UWCCC DSMC: saenotify@uwcarbone.wisc.edu

b. UWCCC PI: Kari Wisinski, MD

c. UWCCC Breast Clinical Team Manager: Tamara Koehn

d. Any other appropriate parties listed on the SAE Routing Form

#### 12.4.1.2 Report to the Sponsor:

Serious adverse events (whether or not related to study drugs) will also be reported to Oncoceutics or designee within 24 hours from the time the Investigator first becomes aware of the SAE. After the initial SAE notification to Oncoceutics or designee, follow-up SAE information will be submitted each time that important follow-up information (e.g., diagnosis, outcome, causality assessment, results of specific investigations) becomes available.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of initiation of therapy through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, must be reported to Oncoceutics. This applies whether or not the event is related to ONC201.

If serious medical occurrences, including death, occur outside of the safety follow-up window established by the protocol and are reported to or observed by the Investigator to be related to the administration of the investigational product, it is the Investigator's responsibility to report this occurrence to Oncoceutics or designee within 24 hours from the time site personnel become aware of the occurrence.

In addition to SAEs, the following reportable events must also be submitted to Oncoceutics within 24 hours from the time the Investigator first becomes aware of them:

- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)

- Occupational exposure (even if not associated with an adverse event)

  Reports should be made to Oncoceutics using FDA form 3500A (MedWatch) or the UWCCC SAE form may be used.
  **Contact information for submission of reportable events to Oncoceutics:**

  **Fax:** 1-844-245-7650
  **Specifying:**
  - PROTOCOL Number
  - SUBJECT Number
  - SITE Number/PI Name
  - SAE/ONSET DATE

12.4.1.3 Report to the IRB:
Consult the UW Health Sciences website (https://kb.wisc.edu/hsirbs/18324#UP) for reporting guidelines.

12.4.2 **SAE Requiring 10 Day Reporting Occurs at UWCCC:**

12.4.2.1 Report to the UWCCC:
Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=54655) for specific instructions on how and what to report to the UWCCC for [10] day reports.
For this protocol, the following entities are required to be notified:

a. UWCCC DSMC: saenotify@uwcarbone.wisc.edu
b. Any appropriate parties listed on SAE Routing form

12.4.2.2 Report to the Sponsor:
See section 12.4.1.2 - SAEs must be reported to Oncoceutics or designee within 24 hours.

12.4.2.3 Report to the IRB:
Consult the UW Health Sciences IRB website (https://kb.wisc.edu/hsirbs/18324#UP) for reporting guidelines.

12.4.3 **SAE Requiring 24 Hour Reporting Occurs at a WON Site:**

12.4.3.1 Report to the UWCCC:
Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP, JC, and other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=54655) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up

reports. A follow-up report is required to be submitted within 5 calendar days of the initial [24] hour report.

Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, in accordance each entities' reporting requirements.**

12.4.3.2 Report to the Sponsor:
The UW Principal Investigator is responsible for ensuring the SAE is reported to the sponsor, Oncoceutics.

12.4.3.3 Report to the IRB:
WON sites should follow their own local IRB reporting guidelines for SAE submission. The UW PI is responsible for the submission of the SAE to the UW Health Sciences IRBs for any site for which the UW serves as the IRB of record. Additionally, the UW PI is responsible for the submission of the SAE to the UW Health Sciences IRB for any site if it meets the definition of unanticipated problem.

12.4.4 **SAE Requiring 10 Day Reporting Occurs at a WON site:**

12.4.4.1 Report to the UWCCC:
Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP, JC, and other Affiliates** on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=54655) for specific instructions on how and what to report to the UWCCC for [10] day reports.

Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu

NOTE: After a WON site has submitted the [10] day SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, in accordance each entities' reporting requirements.**

12.4.4.2 Report to the Sponsor:
The UW Principal Investigator is responsible for ensuring the SAE is reported to the sponsor, Oncoceutics.

12.4.4.3 Report to the IRB:
WON sites should follow their local IRB reporting guidelines for SAE submission. The UW PI is responsible for the submission of the SAE to the UW Health Sciences IRBs for any site for which the UW serves as the IRB of record. Additionally, the UW PI is responsible for the submission of the SAE to the UW Health Sciences IRB for any site if it meets the definition of an unanticipated problem.

## 12.5 Other Reporting Requirements

**Reporting to the FDA**
Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA as determined by the completion of the UW Sponsor-Investigator Determination Form for FDA Reporting of Safety Events. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

# 13. STATISTICAL METHODS

## 13.1 Study design
We propose a phase II clinical trial, non-randomized, single arm, open label study of the combination of ONC201 with of ONC201 with intermittent MR diet in patients with metastatic TNBC.
Accrual is competitive such that each site can contribute any number of subjects until the study maximum of 34is reached.

The primary objective is to evaluate the rate of patients with objective response to ONC201 with a MR diet.

## 13.2 Sample size and accrual
The primary objective is to evaluate efficacy of ONC-201 with dietary MR in metastatic TNBC. The study is designed as a single-arm phase II trial. The primary endpoint is ORR. Secondary endpoints include CBR at 4 months, PFS, OS, safety, metabolic indices and CTC TRAIL-receptor expression. The null hypothesis is that the probability of overall response is no more than 0.1, *i.e.*, $H_0$: $p \leq 0.1$, and the alternative hypothesis is $H_1$: $p \geq 0.25$.

In this single arm study, a Simon's two stage design will be utilized. The null hypothesis that the true ORR is 0.1 will be tested against a one-sided alternative. The study will be powered to detect an ORR of 25% with the combination of ONC201 with a methionine-restricted diet, using a power of 80% and a type I error rate of 10%. The first stage sample size will be 13. After testing the combination on 13 subjects in the first stage, the trial will be terminated if 1 or fewer subjects respond. If the trial goes on to the second stage, a total of 34 subjects will be studied (i.e. additional 21 subjects will be recruited). If the total number responding or having ORR is less than or equal to 5, the combination of ONC201 with a methionine-restricted diet will be rejected.

The estimated total sample size for the study is 34 subjects.

One subject was enrolled to the ONC201 +MR diet prior to changing the dosing schedule. This subject will be replaced for efficacy analysis, but will be considered part of the safety analysis.

## 13.3 Analysis datasets

| Population | Definition |
|---|---|
| Evaluable for Safety | This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation. |
| Evaluable for Efficacy | This will comprise all subjects who receive at least 80% of ONC201 + MR diet doses during the first two cycles of treatment (i.e., at least 9 doses of ONC201) and have at least one disease re-evaluation. Subjects who are not evaluable for response, however, will be replaced. |

## 13.4 Assessment of safety

Any subject who receives at least one dose of treatment on this protocol should be evaluable for toxicity. Safety will be assessed by NCI CTCAE v5.0.

## 13.5 Demographic and baseline characteristics

Descriptive statistics will be provided to summarize demographics and baseline characteristics parameters. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters.

## 13.6 Assessment of efficacy

All subjects who have received at least 80% of ONC201 + MR diet during the first two cycles of treatment and have their disease re-evaluated will be evaluable for assessment of objective response.

## 13.7 Data analysis plan

### 13.7.1 Analysis plans for primary objective

ORR will be estimated according to RECIST 1.1, by dividing the total number of responders (complete plus partial responses plus CR or PR) or (CR or PR), respectively, by number of subjects with measurable disease and the exact 95% confidence interval will be provided. In evaluating ORR, subjects with missing data will be considered non-responders.

### 13.7.2 **Analysis plans for secondary objectives**

PFS and OS will be summarized using Kaplan-Meier estimates of the median survival times. Point estimates as well as 95 % confidence intervals will be provided. PFS based on degree of AR expression by IHC (AR >0% vs. AR ≥10%) will be compared using the log-rank test. Additional exploratory analyses using proportional hazards model to control for other factors may be performed.

CBR at 4 months will be estimated according to RECIST 1.1, by dividing the total number of responders (complete plus partial responses plus CR or PR or stable disease (SD)), by number of subjects with measurable disease and the exact 95% confidence interval will be provided. In evaluating CBR, subjects with missing data will be considered non-responders. Also, duration of response (DOR) will be measured using Kaplan-Meier methodology. A 95% confidence interval will be provided for the median duration of response. Subjects who do not relapse will be censored at the day of the last objective tumor assessment. In evaluating response duration, non-responders will be excluded from analysis.

In addition, correlation analyses will be performed to assess the expression of TRAIL receptor in CTCs prior, during and upon progression of disease. Formal statistical tests will be performed based on the outcome types and the biomarker quantification.

Safety and Tolerability by NCI CTCAE v5.0 will be assessed by frequency tables. Also, metabolic indices in patients with metastatic TNBC treated with ONC-201 and a methionine-restricted diet will be assessed by frequency tables and descriptive statistics.

### 13.7.3 **Analysis plans for exploratory objectives**

Kaplan-Meier methodology will be used to summarize time-to-event data, such as time to development of brain metastases or worsening of brain metastases in patients with metastatic TNBC treated with ONC-201 with a methionine-restricted diet. Graphical techniques (e.g., waterfall plots, KM curves, line plots) may be used when such methods are appropriate and informative.

## 14. TRIAL MANAGEMENT

### 14.1 Data Quality Oversight Activities

Remote validation of OnCore data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable.

The trial site may also be subject to quality assurance audit by Oncoceutics or its designee as well as inspection by appropriate regulatory agencies.

### 14.2 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-will register the trial and post the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

## 15. DATA HANDLING AND RECORD KEEPING

### 15.1 Data Management

UWCCC will serve as the Clinical Research Office for this trial. Data will be collected through the web-based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. UWCCC personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel from participating institutions. The Study Procedures Manual will outline EDC entry guidelines.

### 15.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in OnCore and correlative results will be captured in OnCore or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at UWCCC and is the sole property of the University of Wisconsin. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator.

### 15.3 Record Retention

To enable evaluations and/or audits from Health Authorities, the site investigator agrees to keep records, including the identity of all subjects (sufficient information

to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until UWCCC confirms destruction is permitted.

### 15.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, Oncoceutics, Inc., IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects' identity will remain confidential.

### 15.5 WON Site Oversight

The UWCCC Affiliate Office serves as the coordinating center for WON. Coordinating center responsibilities are shared between the Affiliate Coordinator and UWCCC Breast/Melanoma DOT. A detailed description of coordinating center responsibilities, as well as other WON processes and procedures, is provided in the WON Manual available on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=42878).

Regular communication between the UWCCC Affiliate Office and WON sites ensures that all participating parties are notified of protocol changes, informed consent document revisions, action letters, study status changes, reportable events/Serious Adverse Events (as necessary), and any other applicable information. This communication is accomplished through regular email updates and conference calls.

## 16. ETHICS

### 16.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by the UW IRB. The approved final study protocol and informed consent form will then be provided by the Affiliate Coordinator each participating site to be submitted to each site's local IRB of record.

The UW PI and participating site investigators are responsible for informing their respective IRBs of any amendment to the protocol in accordance with local requirements. In addition, each respective IRB must approve all advertising used to recruit subjects for the study as local regulations require. The protocol must be re-approved by each respective IRB, as local regulations require.

Progress reports and notifications of adverse events will be provided to each respective IRB according to local regulations and guidelines.

### 16.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

### 16.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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