Protocol Title: A Phase II Study of ONC201 in Recurrent or Metastatic Type II Endometrial Cancer

Protocol Number: ONC012 (NCT03485729)

Protocol Date: 11 May 2020 (Version 4.0)

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Protocol Version: 4

Date: May 11, 2020
Replaces:
Version 3 dated 10 April 2018
Version 2 dated 10 January 2018
Version 1 dated 07 September 2017

Oncoceutics Study Identifier: ONC012

Sponsor:
Oncoceutics
3675 Market Street

Philadelphia, PA 19104

Agent(s): ONC201

IND: 121496

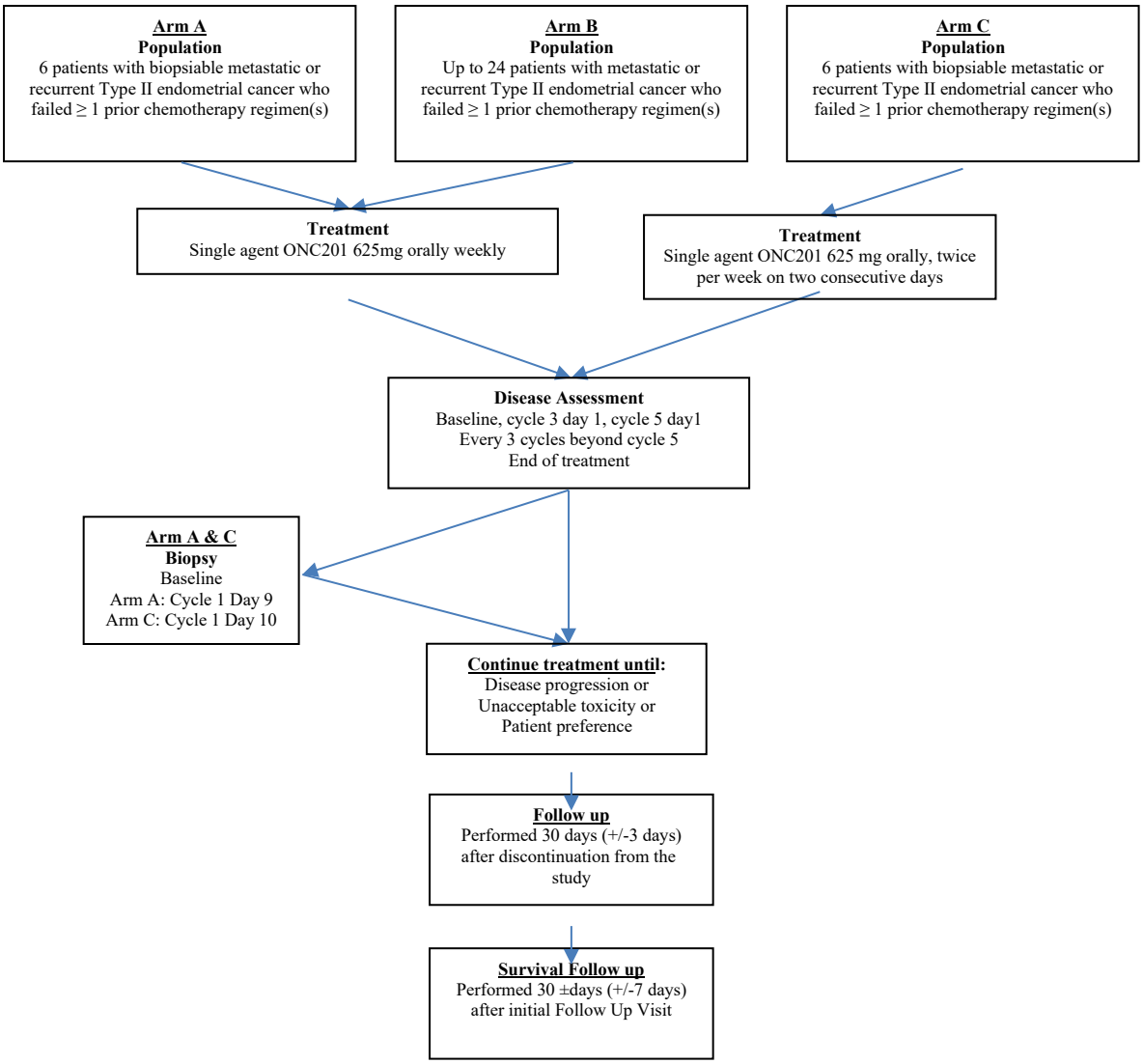
Study Summary

Title	A Phase II Study of ONC201 in Recurrent or Metastatic Type II Endometrial Cancer
Short Title	ONC201 in Type II Endometrial Cancer
Oncoceutics Protocol Number	ONC012
IND	121496
Regulatory Sponsor	Oncoceutics, Inc.
Phase	Phase II
Methodology	A Bayesian method will be used for toxicity monitoring based on the dose-limiting toxicity (DLT) rate.
Study Duration	Approximately 24 months from start of screening to last subject processed and finishing the study

Endpoints/ Objectives	**Primary Objectives:** • To determine efficacy of ONC201 in metastatic type II endometrial cancer **<u>Secondary Objective:</u>** • Evaluation of the safety profile of single agent ONC201 in women with recurrent or metastatic endometrial cancers • Evaluation of intratumoral ONC201 concentrations in women with recurrent or metastatic endometrial cancers **Primary Endpoint**: • Progression-free survival rate at 2 months by RECIST version 1.1. **Secondary Endpoints:** • Safety profile of ONC201 will be determined by type, frequency, severity and timing and relationship of Adverse Events and lab abnormalities to ONC201. • Duration of response and duration of stable disease will be determined by the time-period when a response is first seen or stable disease until disease progression. • Overall response rate by RECIST version 1.1. Median PFS will be calculated as the period between the start of the treatment until disease progression. • Study drug concentration in tumor tissues from patients taking once per week or twice per week on two consecutive days, about 24 hours after the first or second dose respectively
Arms	Arm A and C: Patients with biopsiable metastatic or recurrent Type II endometrial cancer who failed ≥ 1 prior chemotherapy regimen(s). Patients will receive ONC201, 625 mg PO, once every week (Arm A) or twice per week on two consecutive days (Arm C), respectively. Arm B: Patients with metastatic or recurrent Type II endometrial cancer who failed ≥ 1 prior chemotherapy regimen(s). Patients will receive ONC201, 625 mg PO, once weekly.
Major Eligibility	Histologically confirmed metastatic or recurrent Type II EC (serous, clear cell, carcinosarcoma, adenosquamous and mixed histologies) Age ≥ 18 years. ECOG performance status of 0, 1, or 2

Anticipated Number of Subjects	Arm A: 6 patients Arm B: 24 patients Arm C: 6 patients
Study Drug	Oral ONC201 provided as 125mg capsules. Subjects will be treated with oral ONC201 once every week in Arms A and B. Patients in Arm C receive ONC201 625mg twice per week on two consecutive days. A treatment cycle is 3 weeks.
Duration of administration	ONC201 treatment will continue until confirmation of both radiographic and/or clinical disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
Statistical Methodology	Arm A: Intratumoral ONC201 concentration in patients will be summarized using descriptive statistics. Arm B: Simon two-stage, non-randomized, open label, 2-arm Phase II trial of ONC201 in women with metastatic or recurrent Type II endometrial cancer who failed at least 1 prior chemotherapy regimen. Arm C: Intratumoral ONC201 concentration in patients will be summarized using descriptive statistics.

Schema


Arm A
Population
6 patients with biopsiable metastatic or recurrent Type II endometrial cancer who failed ≥ 1 prior chemotherapy regimen(s)
Arm B
Population
Up to 24 patients with metastatic or recurrent Type II endometrial cancer who failed ≥ 1 prior chemotherapy regimen(s)
Arm C
Population
6 patients with biopsiable metastatic or recurrent Type II endometrial cancer who failed ≥ 1 prior chemotherapy regimen(s)
Treatment
Single agent ONC201 625mg orally weekly
Treatment
Single agent ONC201 625 mg orally, twice per week on two consecutive days
Disease Assessment
Baseline, cycle 3 day 1, cycle 5 day1
Every 3 cycles beyond cycle 5
End of treatment
Arm A & C
Biopsy
Baseline
Arm A: Cycle 1 Day 9
Arm C: Cycle 1 Day 10
Continue treatment until:
Disease progression or
Unacceptable toxicity or
Patient preference
Follow up
Performed 30 days (+/-3 days) after discontinuation from the study
Survival Follow up
Performed 30 ±days (+/-7 days) after initial Follow Up Visit

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1 Introduction

1.1 Study Disease

Endometrial cancer is the most common gynecologic malignancy in the United States with 60,050 new cases and 10,470 deaths expected in 2016[1]. Due to a common presentation of postmenopausal vaginal bleeding, most patients are diagnosed with uterine-confined disease (i.e. stage 1)[1] and thus, will have an overall favorable prognosis with 5 year disease-free survival greater than 80%[2]. However, there has been a steady increase in the mortality rate for endometrial cancer which has been attributed to higher proportions of patients with advanced stage, higher grade and serous histology [3].

1.2 Disease Classification & Rationale for Correlative Sampling

In 1983, Bokhman and colleagues introduced a classification system of endometrial cancers based upon two separate tumorigenic pathways which vary by incidence, risk factors and prognosis [4]. Type 1 tumors, which account for 80% of cases, are typically grade 1-2 endometrioid tumors associated with a high estrogen state and have an overall favorable prognosis. Conversely, type 2 tumors, which account for 10-20% of cases, have a less favorable prognosis due to more advanced stage and grade of disease at presentation. Tumors in this group can include grade 3 endometrioid, serous, clear cell, mucinous, squamous, transitional cell, mesonephric and undifferentiated subtypes. Further, endometrial carcinosarcoma are now felt to be dedifferentiated carcinomas consisting of carcinomatous and sarcomatous elements. The carcinomatous elements most commonly contain high grade serous histology, and therefore these tumors could be considered type 2 cancers. While this subtype comprises ~10-20% of all endometrial tumors, type II EC accounts for up to 40% EC-related deaths [4, 5]. Among the non-endometrioid ECs, papillary serous accounts for 17-22% of ECs and clear cell cancer represents 1% to 6% [6]. Type 2 cancers, in particular those of serous histology, may have alterations in *p53*, *p16, E-cadherin*, *HER2/neu, PIK3CA*, *FBXW7*, and *PPP2R1A* [7, 8].

Endometrial serous carcinoma (ESC) is a high-risk cancer having poorer prognosis because it is a fast-growing tumor that infiltrates deeply in the myometrium, and frequently involves lymphovascular space invasion and distant metastases. The 5-year survival rate of ESC patients is 0-30% (Stage III & IV) and 45-90% (Stage I & II). Clear cell carcinoma is usually detected in postmenopausal women, with a mean age of 62-67 years [9]. Grossly clear cell carcinomas often form fleshy and soft masses involving most of the endometrial surface. Microscopically, the neoplasm can exhibit different patterns, namely solid, papillary, tubular and cystic [9]. The clear cytoplasm results from the presence of glycogen, and hobnail cells are cells with a naked nucleus that have discharged their glycogen and lost most of their cytoplasm. Nuclear atypia is usually marked and mitotic activity is high [9]. This subtype comprises of 3% of all EC cases while is responsible for 8% of EC deaths [9].

More recently, The Cancer Genome Atlas Research Network examined 373 recurrent endometrial cancers, including 307 endometrioid, 66 serous and 13 mixed histology cases, in order to better define tumors by genomic, transcriptomic and proteomic characteristics [10]. Based on their analyses, the authors characterized these tumors into 4 groups: *POLE*

ultramutated, microsatellite instability hypermutated, copy-number low and copy-number high. The authors suggest that this "genomic-based classification may lead to improved management of these patients." Further, analysis revealed that the PI3K/Akt/mTOR pathway is the most frequently altered pathway in endometrial cancer, with 93% of type 1 vs. 60% of type 2 exhibiting alterations [10]. Therefore, this pathway may be an appropriate target for therapy in women with recurrent endometrial cancers.

1.3 **Endometrial Cancer Treatment**

The mainstay of treatment is surgical staging, including hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and peritoneal cytology [11]. Chemotherapy and/or radiation therapy may be utilized in patients with early stage disease at high risk for recurrence or in those with metastatic disease. Acceptable systemic chemotherapy options for recurrent, metastatic or high-risk disease include multiagent regimens such as carboplatin/paclitaxel [12], cisplatin/doxorubicin, and cisplatin/doxorubicin/paclitaxel [13]. Carboplatin/paclitaxel is often used as the first line therapy due to its lower toxicity and equivalent efficacy based on the preliminary findings of GOG 209. Response rates for this regimen range from 40-62% with overall survival ranging 13-29 months [12, 14, 15]. Single agent regimens generate response rates ranging 21-36% for first-line therapy vs. 4-27% when used for second-line therapy [16]; the most effective single agent is paclitaxel.

Targeted therapy options have more recently been examined in this population. Single-agent bevacizumab, a monoclonal antibody blocking VEGF-A, was examined in a phase II trial of women with persistent or recurrent endometrial cancers who had failed 1-2 prior cytotoxic regimens [17]. Clinical response rate was 13.5%. Median progression free and overall survival was 4.2 and 10.5 months, and 40.4% survived progression free for at least 6 months.

Agents targeting the PI3K/Akt/mTOR signaling pathway, in particular temsirolimus and everolimus which are rapamycin derivatives that inhibit mTOR, have also been examined in this patient population [18, 19]. Single agent temsirolimus resulted in partial responses in 4 (14%) chemo-naïve patients vs. 1 (4%) patient who had received one prior line of chemotherapy [18]. Clinical outcomes did not correlate with *PTEN* loss or markers of the PI3K/Akt/mTOR pathway. Everolimus was examined in an open label phase 2 trial of everolimus in recurrent endometrioid endometrial cancer patients who failed 1-2 prior regimens [19]. Of 35 evaluable patients, clinical benefit, defined as complete response + partial response + prolonged stable disease (≥8 weeks), was seen in 43% at 8 weeks and 21% at 20 weeks. Results from these trials have been encouraging, and the authors suggest that further investigation is necessary to better define target patient populations as well as combinations with chemotherapy.

1.4 **Agent under Investigation**

ONC201 was discovered in a screen that was performed to identify compounds that would activate cell death in tumor cells but not in normal cells. ONC201 is a first-in-class small molecule that selectively targets the G-protein coupled receptor DRD2 and activates integrated stress response (ISR) in tumor cells to induce tumor cell death. Activation of ISR by ONC201 has dual advantage that leads to downstream anti-cancer effects. ONC201

mediated ISR activation not only leads to inactivation of Akt and Erk pathways, which are pro-survival and proliferation pathways, but also results in activation of TRAIL pathway that results in tumor cell death. These effects of ONC201 have been demonstrated in many *in vitro* as well as *in vivo* experiments. Despite its strong cytotoxicity in tumor cells, ONC201 does not induce cell death in normal cells and this is due to only a partial and transient activation of one of the pathways that does not lead to significant amount of cell death [20] Specifically, activation of ISR in tumor cells decreases protein translation and up regulates ATF4 activation, which in turn is responsible of induction of pro-apoptotic genes. ATF4 also cooperates with CHOP to down-regulate Akt and Erk activation in tumor cells [21, 22].

The safety profile of ONC201 has been studies in lab animal models and the results are very favorable [23]. Exaggerated dosing in rodents and dogs revealed that ONC201 acute toxicity occurs at higher than therapeutic doses. Even at the highest doses tested, the drug did not achieve a maximum tolerated dose with oral administration in GLP studies. Induction of cell death in normal tissues has not been apparent in animal studies with ONC201 even at exaggerated dosing levels.

1.4.1 Clinical safety profile of ONC201

As of 31 December 2019, ONC201 has been administered to more than 250 patients in sponsored trials. Please refer to the most recent Investigator's Brochure for the complete safety profile of ONC201.

1.4.2 Clinical Profile of ONC201

There were signs of clinical activity in the first-in-human trial that enrolled advanced solid tumor patients. After 2 doses of 375mg ONC201, one 72-year-old patient with advanced clear cell endometrial cancer had a mixed response with multiple nodes decreasing by >30% along with the development of new nodes (see Table 1). Another

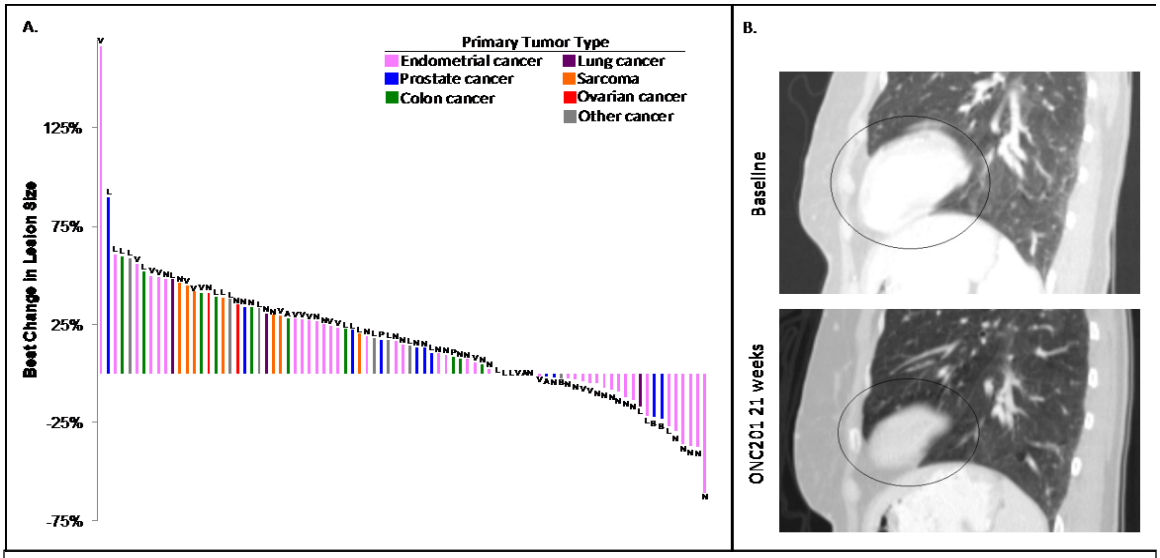


Figure 1. Antitumor activity in metastatic lesions. (A) Waterfall analysis on a lesion-by-lesion basis. Best change in lesion size is defined as the maximal reduction or minimal increase in sum of longest dimensions of target lesions relative to pretreatment assessment. 25/28 patients had measurable tumors at baseline and at least one post-treatment evaluation. Letters above or below bar denotes location of the lesion: V = liver; L = lung; N = lymph node; A = adrenal gland; P = primary tumor; B = bone. (B) Metastatic lung lesion of an endometrial cancer patient at baseline and after 8 doses of 625mg ONC201.

56-year old endometrial cancer patient with poorly differentiated carcinoma with papillary features experienced prolonged stable disease for 10.5 months and exhibited sustained regression of her metastatic lung lesion (Figure 1B). Another 67-year-old patient with advanced endometrioid type EC (5 prior lines of therapy) had stable disease for 4 months. Both these patients had surgery, radiation, immunotherapy and were treated with 5 different chemotherapy regimens, including carboplatin, paclitaxel, doxorubicin and cisplatin. Waterfall analysis of the 28 patients on a lesion-by-lesion basis revealed tumor regressions in prostate and endometrial cancer patients that involved lymph nodes, bone, and lung lesions (Figure 1A).

EC Subtype	ONC201		Best Overall Response	Time on Treatment (weeks)	M30 Induction (>50%)
	Dose (mg)	No. of doses			
Clear cell	375	2	MR	6	Yes
Endometrioid	125	6	SD	18	Yes
Serous	250	14	SD	42	No
Serous	625	2	PD	6	Yes
Endometrioid	625	3	SD	9	No

Table 1: **Tumor responses and pharmacodynamics in the endometrial cancer patients enrolled in the first in human study.** Abbreviations: MR-mixed response, SD – stable disease, PD – Progressive disease

1.4.3 Pharmacokinetics

Pharmacokinetic (PK) analysis was performed in a Phase I dose escalation study in patients with advanced solid tumors. ONC201 was found to have a half-life of 11.3 hours in humans. The dose escalation cohorts consisted of single patient and analysis was done on plasma obtained within 21 days of drug administration. The LC-MS-MS analysis demonstrated that exposure to ONC201 saturated at the dose of 375mg. For the maximum dose tested, which was 625mg, Cmax was determined to be 3312 (SD2133) ng/ml. The Cmax was reached approximately 1.8 hours after the dose administration.

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 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, 500mg 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 2).

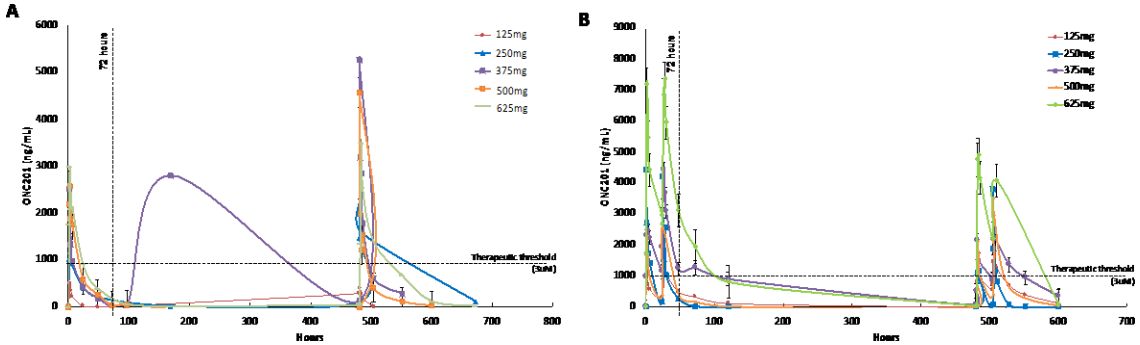


Figure 2. Plasma concentrations of ONC201 administered (A) once per week or (B) twice per week on two consecutive days to adults with relapsed/refractory acute leukemias or high-risk myelodysplastic syndromes. Hour 0 is the baseline sampled before the first dose on ONC201. Error bars reflect SEM of samples from patients enrolled to receive the same dose.

1.5 **Study Rationale**

ONC201 is a small molecule which selectively targets the G protein-coupled receptor DRD2. Downstream of target engagement, ONC201 activates the integrated stress response (ISR) in tumor cell leading to inactivation of Akt and ERK signaling as well as

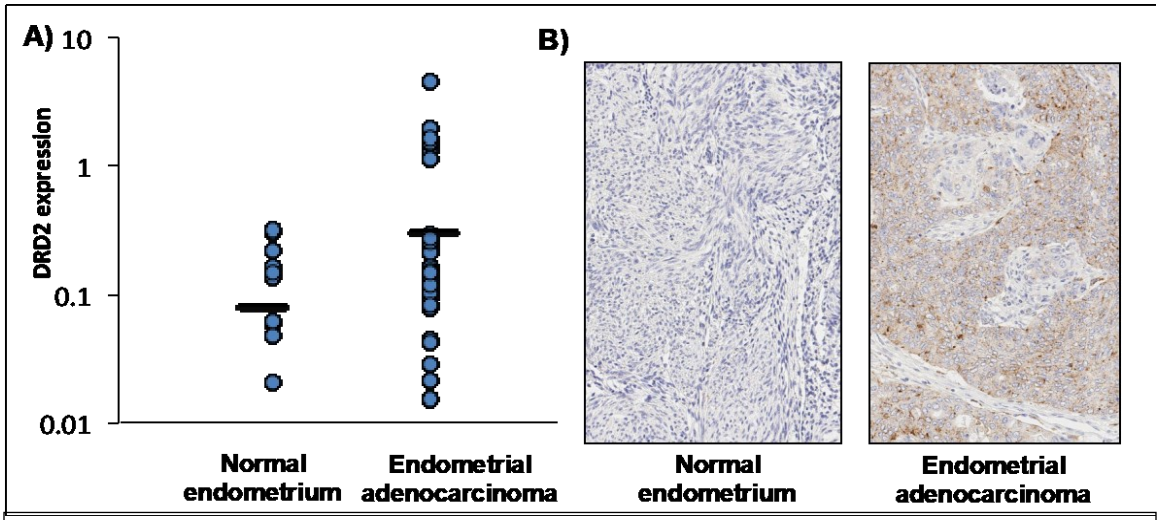


Figure 2. DRD2 expression in human endometrium specimens. A) Average DRD2 expression (% positive area) in normal endometrium (N=11) and endometrial adenocarcinoma (N=32) samples from patient-derived tissue microarrays. B) Representative image of DRD2 expression in normal endometrium and malignant endometrial adenocarcinoma.

induction of the TRAIL pathway [24]. These pathways are highly deregulated in a majority of Type II EC patients. ONC201 also inhibits dopamine receptor 2 (DRD2), resulting in anti-tumor responses in preclinical models [24]. Furthermore, DRD2 expression was several fold higher in endometrial adenocarcinoma when compared to normal endometrium.

Single agent ONC201 has been examined in open-label Phase I studies in patients with advanced, treatment refractory solid malignancies [24, 25]. Due to its differential anti-proliferative and pro-apoptotic response in tumor cells, treatment was overall well tolerated, and the recommended phase II dose of ONC201 was set at 625mg every three weeks. An additional dose-escalation phase I study (NCT02609230) is further evaluating weekly versus three-week dosing in patients with advanced solid tumors and multiple myeloma. Preliminary data from these phase I studies suggests a possible clinical benefit in patients with advanced, chemo-refractory endometrial cancers, with at least one mixed response noted in a patient with clear cell histology [17].

We hypothesize that single agent ONC201 will demonstrate clinical benefit in women with recurrent or metastatic type II endometrial cancers.

Systemic exposure with once per week dosing in patients results in concentrations that exceed the 1,000ng/mL threshold for ~24 hours. 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. This generated the hypothesis that

consecutive day dosing could maintain therapeutic concentrations for >48 hours. As summarized in Section 1.4.3, PK results from a Phase I/II indicate that twice per administration of ONC201 on two consecutive days maintains >1,000ng/mL systemic concentrations for >72 hours in patients who received 375mg or 625mg. Given the safety profile of ONC201 and these findings, the safety of twice per week dosing on two consecutive days will be evaluated in this clinical trial in addition to weekly dosing.

1.6 Correlative Testing

Correlative testing will be performed on archival tumor tissue, tumor biopsies and blood collected pre- and post- treatment. Tumor tissue and blood samples will be used to test the markers of response to ONC201 treatment. The status of these markers will be used to correlate with treatment outcome. Refer to section 8.0 for details.

2 Objectives

2.1 Primary Objective

Determine the efficacy of single agent ONC201 dosed 625mg orally in women with metastatic or recurrent endometrial cancer at 2 months after treatment initiation.

2.2 Secondary Objectives

Evaluation of the safety profile of single agent ONC201 in women with recurrent or metastatic endometrial cancers.

2.3 Primary Endpoint

Progression-free survival rate at 2 months by RECIST version 1.1.

2.4 Secondary Endpoints

- Safety profile of ONC201 will be determined by type, frequency, severity and timing and relationship of Adverse Events and lab abnormalities to ONC201.
- Duration of response and duration of stable disease will be determined by the time-period when a response is first seen or stable disease until disease progression.
- Overall response rate will be determined by RECIST version 1.1. Median PFS will be calculated as the period between the start of the treatment until disease progression.
- Study drug concentration in tumor tissues from patients taking once per week or twice per week on two consecutive days, about 24 hours after the single dose or second dose respectively.

3 Study Plan

We propose a Simon two-stage, non-randomized, open label, Phase II trial of ONC201 in women with metastatic or recurrent Type II endometrial cancer who failed at least 1 prior chemotherapy regimen. Patients with histologically confirmed Type II endometrial cancer,

including but not limited to serous, clear cell, carcinosarcoma, adenosquamous, and mixed histologies, will be eligible.

Arm A and C will enroll 6 evaluable patients each. All subjects in Arm A will have a biopsy of their tumor one day after the second dose of ONC201 on Cycle 1 Day 9. All subjects in Arm C will have a biopsy of their tumor one day after the 4th dose of ONC201 on Cycle 1 Day 10.

Arm B will enroll 10-24 evaluable patients.

ONC201 will be administered at a dose of 625 mg by mouth, once or twice each week until disease progression, unacceptable toxicity, or if the patient discontinues for any other reason.

It is anticipated that enrollment into this study will complete in 24 months.

Radiologic tumor assessment will be performed at baseline, cycle 3 day 1, cycle 5 day 1 and at the end of every 3 cycles beyond cycle 5 (one cycle = 21 days). All patients including those removed from the study due to unacceptable toxicity, will undergo radiologic tumor assessment within 30 days of the time of discontinuation (End of treatment). If a scan is performed within 30 days of end of treatment is available, the previous scan will be accepted. Patients who show disease progression at the first instance could continue to receive the treatment for up to 2 more cycles depending upon the percentage of increase in the tumor. Patients up to 30% increase in tumor burden would be allowed to continue the treatment until the second confirmatory scan if the patient is deriving clinical benefit in the treating Physician's opinion. Patients who continue treatment beyond progression would undergo another confirmatory scan at the end of 2 more cycles and if the progression is confirmed they will be come off the study.

4 Eligibility Criteria

4.1 Inclusion Criteria

1. Histologically confirmed metastatic or recurrent Type II EC (serous, clear cell, carcinosarcoma, adenosquamous and mixed histologies). For patients with tumors that have mixed histologies, the tumor should have evidence of some tumor cells with Type II endometrial cancer features.
2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 as described in detail in section 11.
3. Availability of at least 12 unstained slides from archival FFPE tumor tissue. Available archived tissue biopsies will be provided for correlative studies.
4. For Arm A and C, patients must have disease that is amenable to biopsy and must be willing to provide consent for a tumor biopsy at baseline (within 30 days of beginning ONC201) and at least 1 on-treatment tumor biopsy.
5. Must have radiographic disease progression after at least 1 line of systemic cytotoxic therapy for metastatic disease or with progression within 12 months of completing adjuvant chemotherapy.

6. Age $\geq$ 18 years.
7. ECOG performance status of 0, 1, or 2.
8. Patients must have adequate bone marrow, hepatic and renal function as defined below:

Leukocytes	$\geq$ 3,000/mcL
Absolute neutrophil count	$\geq$ 1,500/mcL
Platelets	$\geq$ 100,000/mcL
Total bilirubin	$\leq$1.5 ULN
AST/ALT (SGOT/SGPT)	$\leq$ 2 ULN
Creatinine	$\leq$1.5 ULN
OR	
Creatinine clearance	$\geq$ 60 Ml/min/1.73 m^2 for patients with creatinine levels above ULN calculated using Calvert formula

9. Life expectancy at least 3 months.
10. Ability to understand and willingness to sign a written informed consent and HIPAA consent document.
11. Patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment.

4.2 Exclusion Criteria

1. No prior treatment with ONC201.
2. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
3. The subjects who have not recovered to baseline or CTCAE $\leq$ Grade 2 from related toxicity to all prior therapies will be excluded. Patients with Non-serious adverse events such as alopecia, fatigue, weakness, loss of appetite and nausea that are non-significant will not be excluded.
4. Any other prior malignancy from which the patient has been disease free for less than 3 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of any site.
5. The subject is unable to swallow capsules.
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of ONC201 (uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

7. Patients receiving any other investigational agents.
8. Patients with symptomatic brain metastases are excluded. Patients with asymptomatic and treated CNS metastases may participate in this trial. The patient must have completed any prior treatment for CNS metastases > 28 days prior to study entry including radiotherapy or surgery. Steroids for the treatment of brain metastasis are not permitted, and patients must be stable off steroid treatment for 4 weeks prior to enrollment.
9. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.
10. Active inflammatory gastrointestinal disease, chronic diarrhea (unless related to underlying malignancy or prior related treatment) or history of abdominal fistula, gastrointestinal perforation, peptic ulcer disease, or intra-abdominal abscess within 6 months prior to study enrollment. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.
11. Known HIV-positive patients on combination antiretroviral therapy.
12. Active HBV or HCV infection. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.
13. Pregnant or breast feeding. Refer to section 4.4 for further details.
14. Known history of cardiac arrhythmias including atrial fibrillation, tachyarrhythmias or bradycardia, unless arrhythmia is controlled and after Cardiology has cleared patient to receive ONC201. Receiving therapeutic agents known to prolong QT interval will be excluded, however the use of Zofran is permitted. History of CHF, or MI or stroke in the last 3 months will be excluded.
15. Concomitant use of potent CYP3A4/5 inhibitors or inducers during the treatment phase of the study and within 72 hours prior to starting study drug administration.

4.3 **Inclusion of Women and Minorities**

Women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 **Pregnancy**

The effects of ONC201 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential (WOCBP) must agree to use adequate contraception prior to study entry, for the duration of treatment, and for at least 3 months after the completion of treatment.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a

bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

All WOCBP must have a negative pregnancy test within *72 hours* prior to receiving the first dose of the investigational agent. If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

4.5 Screening Procedures

After providing informed consent, subjects will undergo screening for eligibility to participate in the study. Screening will start within 14 days prior to the first dose of ONC201. Subjects who have had an adequate MRI/CT Scan performed as part of routine care prior to informed consent but within 30 days of the first dose of ONC201 will not have to repeat the baseline MRI. Best efforts should be made to keep the MRI/CT Scan technique constant for each patient from baseline and throughout treatment. Refer also to the Schedule of Events for details of study procedures.

The following procedures will be performed or obtained at screening for the purpose of determining study eligibility. Screening studies, if performed within 2 weeks prior to start of treatment, are acceptable for use as baseline (pre-Cycle 1, Day 1 assessments).

Screening Assessments:

Pathology report confirming the diagnosis of Type II Endometrial Cancer

Collection of archived tumor material for research: 12 unstained slides from archival FFPE tumor tissue. Available archived tissue biopsies will be provided for correlative studies additional details on tumor material collection in the Eligibility Criteria (Section 4).

A MRI/CT Scan must be obtained within 30 days of the first dose of study treatment.

Medical history, eligibility, and concomitant medications: The subject must be eligible by all of the Subject Selection Criteria per Section 4. Concomitant medications will be reviewed for allowed or prohibited medications.

Heart Rate (BPM; recorded from the ventricular rate).

Physical exam and laboratories: For complete details see the Schedule of Events.

Complete physical exam, including ECOG assessment

Vital signs: height (height is only required at screening), weight, temperature, resting blood pressure, pulse and respiration rate.

Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, random glucose, albumin, total protein, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, lactate dehydrogenase (LDH).

Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count

Coagulation test (required at screening only): PT/INR, PT, PTT

Ca125: Per standard of care

Pregnancy test (urine or serum β-HCG) for women of child-bearing potential

4.6 **Subject Registration**

In order to begin the patient registration process, the site must obtain a slot for the candidate patient from Oncoceutics. At the time of receipt of the signed consent form, Oncoceutics medical monitor must be notified via email to initiate eligibility review. The study staff must include de-identified patient source documentation, the completed New Patient Registration Form (provided by Oncoceutics) and a tentative therapy start date. Correspondence from the Sponsor for patient registration approval will be granted within 48 hours of receipt of adequate documentation.

Registration approval will be valid for 7-business days from receipt of approval. If the potential patient is not treated within those 7 business days, a new registration form must be submitted to determine eligibility.

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

5 Treatment Plan

Treatment will be administered on an outpatient basis. Treatment will be administered as described below. Dose delays and modifications should only be done following protocol guidelines described in section 6.0. If treatment delays are more than 14 days due to toxicity study therapy will be discontinued.

5.1 Treatment Administration

Regimen description					
Arm	**Agent**	**Dose**	**Route**	**Schedule**	**Cycle Length**
A & B	ONC201	625mg	Oral	Once per week	3 weeks
C	ONC201	625mg	Oral	Twice per week on two consecutive days	3 weeks

One treatment cycle will be defined as 21 days, corresponding to 3 doses of ONC201 (i.e., one cycle is 3 weeks) for Arm A and B or 6 doses in Arm C. Beyond cycle 1 week 1 dose(s), ONC201 capsules will be dispensed on day 1 of every cycle thereafter to be taken at home. Patients must complete study drug diary to keep a log of the drug intake. Any unused drug should be returned to the site. Any missed doses should be recorded. At home patients must take the drug as indicated, however if the drug is missed for reasons not related to adverse events +/- 2 days are allowed. The capsules should be swallowed as whole and should not be chewed or broken.

Patients should take designated capsules of ONC201 at approximately the same time on each drug administration. Patients will be instructed to not eat for 2 hours pre and 2 hours post dosing. If the patient vomits after taking ONC201, they should not retake the dose.

5.2 Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

In vitro cytochrome P450 assays were conducted in human hepatocytes. In these studies, ONC201 is not an inducer of the CYP450 system (CYP 1A2, 2B6 and 3A4). ONC201 was observed to be a mild inhibitor of the CYP450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) at 35-429uM, i.e. at least 3.5-fold above the Cmax observed in the first-in-human trial. Studies in human liver microsomes indicate that ONC201 appears to be a major substrate of CYP3A4 and a minor substrate of CYP 2B6, 2C8, 2C9 and 2D6. The protein binding of ONC201 was found to be 89.8-94.0% in human plasma over the concentration range of 0.5 μM to 20 μM with similar findings in other species (mouse 86.2-89.6%, rat 79.4–83.1%, dog 88.0-89.8%).
Concurrent use of strong inhibitors or inducers of CYP3A4, 2D6, 1A2, 2C9 and 2C19 should be avoided.

5.2.1 Corticosteroids

The use of systemic corticosteroids should be limited to ≤ physiologic replacement doses (i.e. prednisone 10 mg/day or equivalent). Short courses of higher dose systemic steroids (to treat COPD, for example), are permitted but should be used with caution as no formal interaction studies have been completed. Use of non-systemic steroid use is permitted (e.g. cream, lotion, inhalers).

5.2.2 Anti-emetic Therapy

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

5.2.3 5.2.3 Other Anticancer or Experimental Drugs

Treatment with other anticancer or experimental drugs is not permitted for patients treated on this protocol.

5.2.4 5.2.4 Palliative and supportive care

All palliative and supportive care necessary for optimal care of the patient, excluding radiation therapy should be provided while on study. Patients requiring radiation therapy for palliation will be removed from the study. Treatment with growth factors is excluded except to treat febrile neutropenia.

5.3 Duration of Therapy

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

Confirmed radiographic disease progression. In the absence of clinical progression and occurrence of radiographic progression, patients will have the option to remain on study.

Intercurrent illness that prevents further administration of treatment

Unacceptable adverse events

Patient required > 2 dose reductions

Patient becomes pregnant

Patient decides to withdraw from the study

General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow up

All subjects will be followed post-treatment until death, withdrawal of permission to record at least survival data, or subject is lost to follow-up every 30 days (±7 days) after coming off study. When available, tumor imaging will be collected for all patients who accrued to the study and receive at least one dose of ONC201. All subjects will be contacted every 30 days to assess for study-treatment related toxicities, initiation of any new anti-cancer treatments, and survival status. Contact may be performed by a site visit, telephone contact, e-mail, or mail. The date of death, initiation of any new anti-cancer treatments and date of last contact should be documented if this information is available.

5.5 Criteria for Discontinuation

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. Patients can also be removed from the study for non-compliance. The reason for study removal and the date the patient was removed must be documented in the medical record and case report form.

6 Dose Modifications

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications

Below are dose modifications (Table 6.1 and 6.2) for adverse events that are attributable to study drug, including: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. If a patient experiences other adverse events, or several adverse events and there are conflicting recommendations based on Grade, the investigator will use the recommended dose adjustment that reduces the dose. Dose modifications will be made based on an adverse event that occurs during any time during a cycle.

Criteria for disrupting treatment, dose modification, or discontinuation are listed in Table 6.1. Dose modifications are per the clinical judgment of the investigator and agreement of the subject, the treatment will be resumed according to the table below. Dose modification may not be required for adverse events that are clinically manageable.

Table 6.1 Dose adjustment rules for Adverse Events (AEs), including Nausea, Diarrhea, Neutropenia, Thrombocytopenia, and Other AEs. Alopecia does not require dose adjustments.

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

Participants who experience an adverse event that requires a treatment delay or dose reduction should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution. If a grade 3 or 4 adverse event does not resolve within 3 weeks, the patient will be required to come off study, and the interval for testing may be reduced after consultation and written approval by Sponsor.

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

7 Study Agent 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 and additional excipients may be used.

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.

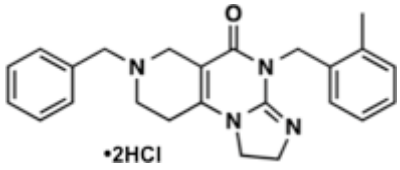
Storage: Preserve in original tightly closed containers at room temperature (15 to 30°C)

Sponsor: Oncoceutics, Inc.

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

7.1 Drug Substance Description

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

Molecular Weight	386.49 (free base) 459.41 (salt)
Molecular Structure	

7.2 Drug Product Description

7.2.1 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 10 or 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.

7.2.2 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 at 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.

7.3 Drug Product Supply, Administration and Inventory

7.3.1 Handling

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

7.3.2 Availability

ONC201 is provided by the Sponsor, Oncoceutics

7.3.3 Administration

Patients will receive ONC201 while in the clinic on day 1 of each cycle. They will take ONC201 as inidcated. The study drug, ONC201, will be supplied in capsule form for oral dosing.

Patients should take the dose of ONC201 specified by their physician 2 hours prior or 2 hours following food or a meal. If the patient vomits after taking ONC201, they should not retake the dose. Missed doses will not be made up, if more than 2 days from the intended day of administration. A pill diary will be provided to the patient to record dosage, time of administration and side effects.

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

7.3.4 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).

7.3.5 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.

8 Biomarker, Correlative and Special Studies

8.1 Tumor biopsy studies

Archival tumor tissue will be required for correlative testing (12 FFPE slides). For Arm A and C, tumor tissue from baseline and on-treatment biopsies (12 FFPE slides each) will be required. The archival tumor tissue will be used for immunohistochemistry (IHC) to test for markers of response to ONC201 that are involved in its mechanism of action such as DRD2, DRD5, ClpP etc. The baseline and on-treatment tumor tissue from Arm A will be used for pharmacodynamic studies. Pharmacodynamic biomarkers include but are not limited to ATF4, CHOP, DR5, cleaved caspase-8, cleaved caspase-3, and DNA fragmentation.

For patients in Arm A and C, biopsied tumor tissue will be obtained from at least 3 core needle biopsies. Tissue will be used for three distinct analyses: intratumoral drug

concentration, nucleic acids, and pharmacodynamic analyses. Two of the three tissues will be flash frozen and the other sample will be formalin-fixed and paraffin-embedded tissue blocks will be prepared for immunohistochemistry. The tissue will be assayed for the following markers that have been implicated in the mechanism of action of ONC201 such as DRD2, DRD5,ClpP, TGM2, KSR1, ATF4, CHOP, pAkt, pERK, TRAIL, and DR5 (Allen et al., 2013a; Ishizawa et al., 2016; Kline et al., 2016). In addition, immune cell phenotyping may also be assessed in the tumor specimens.

8.2 **Blood for pharmacodynamics analyses**

Prolactin and other proteins will be measured in serum as pharmacodynamic markers. One red-top tube (without anti-coagulant) of blood will be collected at the following time points:
For Arm A and Arm B: Blood draws taken at baseline (pre-dose), 2 hours ± 15 minutes, 24 ± 1 hours, 48 hours ± 3 hours, 72 hours ± 12 hours, and Day 8 and 15 ± 24 hours following the first administration of ONC201. Blood will also be collected pre-dose for Cycle 2, Cycle 3 and every odd cycle beyond Cycle 3.
For Arm C: Blood draws taken at baseline (pre-dose), 2 hours ± 15 minutes, 24 ± 1 hours (pre-day 2 dose), 26 ± 2 hours, 48 hours ± 3 hours, 72 hours ± 12 hours, and Day 8 and 15 ± 24 hours following the first administration of ONC201. Blood will also be collected pre-dose for Cycle 2, Cycle 3 and every odd cycle beyond Cycle 3.

Refer to lab manual for collection window of samples. Blood will also be collected at the end of treatment visit for correlative studies. Immune cytokines and effectors will be assessed on serum samples obtained for pharmacodynamic analyses.

Refer to lab manual for Biospecimens processing and handling requirements.

8.3 **Blood for immune cell studies**

Peripheral blood mononuclear cells (PBMCs) will be harvested and investigated for effects of ONC201 on the immune system. One EDTA tube of blood will be collected at the same time points as the red-top tubes are collected: Baseline and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8; Cycle 1 Day 15; pre-dose for the first day of cycle 2, cycle 3 and every odd cycle beyond cycle 3. Blood will also be collected at the end of treatment visit for correlative studies. Collection of PBMCs is not required for Arm C.

8.4 **Blood for pharmacokinetics**

The plasma obtained prior to the isolation of PBMCs (see Section 8.3) will be used to determine concentration of ONC201. No additional blood samples will be collected from the patient for these studies. For Arm C, plasma for pharmacokinetics will be collected at baseline (pre-dose), 2 hours ± 15 minutes, 24 ± 1 hours (pre-day 2 dose), 26 ± 2 hours, 48 hours ± 3 hours, 72 hours ± 12 hours, and Day 8 and 15 ± 24 hours following the first administration of ONC201. Blood will also be collected pre-dose for Cycle 2, Cycle 3 and every odd cycle beyond Cycle 3.

9 Study Calendar

Study visits and procedures may be scheduled with a +/- 2 business day window except for Screening procedures (-14 days) and neuroimaging (MRI/CT) Screening, Cycle3 and every odd cycle day 1 (+/- 7 days). One treatment Cycle is defined as 3 weeks (21 days).

Study Activity	Screening	C1D1	C1D2	C1D3	C1D8	C1D9	C1D10	C1D15	C1D16	C2D1	C2D2	Cycle 3, and every odd cycle, day 1[8]	Off-treatment	Follow-up 30 days (+/- 3 days)[5]	Survival Follow Up (30 +/- 7 days)
Informed Consent	X														
Medical History	X														
Inclusion/exclusion criteria	X														
Concurrent meds[1]	X	X								X		X	X		
Physical exam	X	X								X		X	X		
Performance Status	X	X								X		X	X		
Vital Signs	X	X			X					X		X	X		
Serum Pregnancy test	X	X											X		
ONC201 Administration[8]		X	X		X	X		X	X	X	X	X			
Toxicity Assessment[1]		X			X					X		X	X		
Serum Chemistry[2]	X	X								X		X	X		
Radiological tumor assessment (CT/MRI contrast scans/C/A/P)	X	X										X	X		
Hematology[3]	X	X								X		X	X		
Coagulation tests: PT/INR, PT, PTT	X														
Blood draws for PK/PD[3a]		X	X	X	X			X		X		X	X		
Archived tumor tissue	X														
Tumor biopsy	X					X[4]	X[4]								
Ca125[6]	X	X								X		X	X		
Survival Follow Up[7]														X	X

[1] Toxicity/Concomitant Medication Assessment: Will be performed at each patient encounter
[2] Serum Chemistry: K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin, creatinine, amylase, ALP, bicarbonate, glucose, urea, BUN, phosphorous albumin, total protein: Beginning of each cycle
[3]Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count will be collected at screening, day 1 of treatment cycles, at end of treatment visits and initial follow up visit for all subjects
[3a]Blood for PK/PD: must be processed within 2 hours of collection. **For Arm A and Arm B:** Blood draws taken at baseline (pre-dose), 2 hours ± 15 minutes, 24 ± 1 hours, 48 hours ± 3 hours, 72 hours ± 12 hours, and Day 8 and 15 ± 24 hours following the first administration of ONC201. Blood will also be collected pre-dose for Cycle 2, Cycle 3 and every odd cycle beyond Cycle 3. **For Arm C:** Blood draws taken at baseline (pre-dose), 2 hours ± 15 minutes, 24 ± 1 hours (pre-day 2 dose), 26 ± 2 hours, 48 hours ± 3 hours, 72 hours ± 12 hours, and Day 8 and 15 ± 24 hours following the first administration of ONC201. Blood will also be collected pre-dose for Cycle 2, Cycle 3 and every odd cycle beyond Cycle 3.
[4] Tumor Biopsies: For patients in Arm A, tumor biopsy tissue will be collected at screening/baseline (within 30 days of beginning ONC201) and tumor biopsy tissue will be collected at cycle 1 day 9 (approximately 24 hours after 2nd dose). For patients in Arm C, tumor biopsy tissue will be collected at screening/baseline (within 30 days of beginning ONC201) and tumor biopsy tissue will be collected at cycle 1 day 10 (approximately 24 hours after 4th dose).
[5] Follow-up: Patient will be followed every 30 days until withdrawal of permission to record or death. The initial follow-up visit must occur within 30 days (+/- 3 days) from EOT visit. Copies of clinical imaging might be obtained after discontinuation of ONC201. Information should be collected to assess study-treatment related toxicities, initiation of any new anti-cancer treatments, and survival status. Contact may be performed by a site visit, telephone contact, e-mail, mail or review of medical records. This information should be updated in the patient record and eCRFs.
[6] Ca125 measurement will be carried out at discretion of physician.
[7]Survial Follow Up: Every 30 days (+/- 7 calendar days) from initial Follow up visit. All patients will be contacted every 30 days to assess for study-treatment related toxicities, initiation of any new anti-cancer treatments, and survival status. Contact may be performed by a site visit, telephone contact, e-mail, mail or review of medical records. This information should be updated in the patient record and eCRFs.
[8]For Arm A and B ONC201 administration is on Day 1, 8 and 15 of each 3-week cycle. For Arm C, ONC201 administration is on Days 1, 2, 8, 9 15 and 16 of each 3-week cycle.

10 Adverse Events: List and Reporting Requirements

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol- specified procedure, whether or not considered related to the medicinal product or protocol- specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the ONC201, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to onset of menses or menopause occurring at a physiologically appropriate time.

Adverse events may occur during the course of the use of ONC201 product in clinical trials or within the follow-up period specified by the protocol, from overdose (whether accidental or intentional), from abuse and from withdrawal. Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event.

All adverse events will be recorded from the time the date of initiation of study therapy through 30 days following cessation of treatment and at each examination. Serious Adverse Events will be followed through 90 days following cessation of treatment. Both Adverse events and Serious Adverse Events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol- specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. All Adverse Events regardless of seriousness or relationship to the Investigational Product will be recorded in the Case Report Forms. Serious Adverse Events should be reported per the requirements described in Section 10.1.

10.1 Definitions

Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect. Important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.2 **Reporting of Serious Adverse Events**

Serious Adverse Events: A serious adverse event is any adverse event occurring at any dose or during any use of ONC201 that:
Results in death;
Is life threatening;
Results in persistent or significant disability/incapacity;
Results in or prolongs an existing inpatient hospitalization;
Is a congenital anomaly/birth defect;
Is a new cancer (that is not a condition of the study);
Is associated with an overdose;
Is another important medical event

Progression of the cancer under study is not considered an adverse event.

Any serious adverse event, or follow up to a serious adverse event, including death (beyond 30 days from last dose) 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 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to ONC201, must be reported within 24 hours to Oncoceutics. Deaths, including those from disease progression that occur within 30 days of the last dose of ONC201 must be reported to Oncoceutics within 3 days of acknowledgment of patient status.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to ONC201 that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to Oncoceutics.

Investigators **must** report to Oncoceutics any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 3 days of the last dose of treatment on the Sponsor provided SAE form.

SAE reports and any other relevant safety information are to be forwarded to the pharmacovigilance@oncoceutics.com and the Oncoceutics facsimile number within 24 hours of learning of its occurrence: 1-844-245-7650

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

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

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

10.3 Expected Toxicities

Updated toxicity information can be found in the Investigator's Brochure. Please refer to this document for expected toxicities and associated frequencies.

10.4 Adverse Events Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:

Definite – The AE is clearly related to the study treatment.
Probable – The AE is likely related to the study treatment.
Possible – The AE may be related to the study treatment.
Unlikely – The AE is doubtfully related to the study treatment.
Unrelated – The AE is clearly NOT related to the study treatment.

10.5 Pregnancy

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the site Investigator must immediately notify Oncoceutics.

11 Efficacy

11.1 Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria will be used for objective tumor response assessment. Response assessment would be performed at C3D1, C5D1 and at the end of every 3 cycles beyond cycle 5. All patients, including those removed from the study due to unacceptable toxicity, would undergo radiologic tumor assessment at the time of discontinuation (End of treatment). Patients who show disease progression at the first instance could continue to receive the treatment for up to 2 more cycles if the increase in tumor burden is up to 30%. Patients who continue treatment beyond

progression would undergo another confirmatory scan at the end of 2 more cycles, and if the progression is confirmed, they will be come off the study.

11.2 **Definitions**

Evaluable for adverse events. All patients will be evaluable for adverse events from the time of their first treatment with ONC201.

Evaluable for progression-free survival. All Arm B patients who have received at one dose of ONC201 will be considered evaluable for progress-free survival as the primary endpoint.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.3 **Disease Parameters**

Measurable disease. 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).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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.

Non-measurable disease. 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 patient, these are preferred for selection as target lesions.

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.

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.

11.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope

of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.5 **Response Criteria**

11.5.1 Evaluation 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

11.5.2 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)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient 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 treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD /not evaluated	No	PR	
SD	Non-CR/Non-PD /not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Progression-free survival (PFS) is defined as the time from registration to objective disease progression or death, whichever occurs first. PFS2 will be defined as the percentage of patients who exhibit PFS for >8 weeks (>56 days). Patients who have not progressed or died and are lost to follow up at 2 months will be replaced.

12 Statistical Considerations

12.1 Primary Endpoint and Interim analyses

Arm A and C will assess intratumoral drug concentrations and pharmacodynamics. . Arm B will assess progression-free survival rate at two month following treatment initiation as primary endpoint. Patients with biopsiable disease may represent a biased subset of the overall target population since some sites of metastases will not be amenable to biopsy and therefore comparing these patients' outcomes to historical controls may not be appropriate. For this reason, only patients in Arm B will be evaluated for the primary endpoint of PFS2.

No interim analyses will be performed for Arm A or C. Pharmacodynamic effects will be evaluated by assessment of tissue biomarkers based on mechanism of action and preclinical tumor cell sensitivity studies. IHC analyses for biomarkers such as ATF4, CHOP, and DR5 will be summarized using descriptive statistics.

Intratumoral ONC201 concentration in patients will be summarized using descriptive statistics separately for Arm A and C. The targeted mean intratumoral drug concentration of ONC201 is 2.9 μM, since this represents the mean IC50 of ONC201 in cancer cell panels profiled for in-vitro efficacy. The null hypothesis is set at a mean of 0.0 and the alternative hypothesis is set at a mean of 1.4 to account for an estimated standard deviation of 1.0. A sample size of 6 for each arm achieves 80% power to detect this difference of -1.4 between the null hypothesis mean and the alternative hypothesis with a significance level (alpha) of 0.05000 using a two-sided one-sample t-test. This assumes a normal distribution for this measurement, which is consistent with prior experience.

Below you will find a table with calculations of minimal effect size corresponding to differing SDs for a sample size of 6 patients at 80% power and a two-sided alpha of 0.05. Power is the probability of rejecting a false null hypothesis. It should be close to one. N is the size of the sample drawn from the population. To conserve resources, it should be small. Alpha is the probability of rejecting a true null hypothesis. It should be small. Beta is the

probability of accepting a false null hypothesis. It should be small. Mean0 is the value of the population mean under the null hypothesis. It is arbitrary. Mean1 is the value of the population mean under the alternative hypothesis that is relative to Mean0. Sigma is the standard deviation of the population that measures the variability in the population. Effect Size, |Mean0-Mean1|/Sigma, is the relative magnitude of the effect under the alternative.

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

Arm B uses a Simon two-stage mini–max design [27] to evaluate the hypothesis that ONC201 will extend progression-free survival at 2 months beyond historical controls for this disease, as performed for buparlisib (NCT01397877). Historical controls for type II endometrial cancer show the null hypothesis to be 40% progression free survival at 2 months. To show the alternative hypothesis that >70% of patients exhibiting progression-free survival at 2 months with 90% power and an alpha= 5%, 24 evaluable patients are required for this arm. The probability for early termination under the null hypothesis is 63.3%.

An interim futility analysis will be performed for Arm B when the 10 evaluable patients in Arm B are evaluable for PFS2, as defined in section 11.7. In stage 1 of the study, if at least 5 of the first 10 evaluable patients exhibit progress-free survival for at least two months from treatment initiation (as defined in section 11.7), recruitment will be continued until a total of 24 evaluable patients have been enrolled for this arm. In stage two, if at least 14 patients demonstrated progress-free survival at 2 months ONC201 will be considered to have shown sufficient efficacy to warrant further study.

12.2 **Analysis of Secondary/Exploratory Endpoints**

All patients enrolled in the study who received at least 1 dose of ONC201 will be evaluated in the safety analysis using descriptive statistics including pre-treatment characteristics and concomitant treatment.

Adverse events and clinical labs will be graded according to NCI CTCAE Version 4.03. For labs without CTC grade definitions, results will be summarized as normal, abnormal or not done. Summary tables will present frequencies of patients experiencing at least one AE categorized by System Organ Class and Preferred Term according to MedDRA terminology. Listings will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment. Graphic displays and shift tables may be provided, as appropriate, to illustrate the results over time on study. ONC201 dose delays, dose modifications, drug exposure and duration of treatment will be also summarized.

Duration of response and duration of stable disease will be characterized using Kaplan-Meir estimates in the relevant subgroups.

Progression Free Survival (PFS) will be characterized using Kaplan-Meier curves. Median PFS will be calculated along with 95% confidence intervals. Patients who are lost to follow-up (who withdraw from the study prior to evidence of progression or death) will be censored.

12.3 **Reporting and Exclusions**

12.3.1 Evaluation of toxicity:

All patients will be evaluable for toxicity from the time of their first treatment with ONC201. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received ONC201, including serious adverse events (SAEs). Other safety endpoints include laboratory safety assessments, vital signs and physical examinations.

A Bayesian method [27] will be used for toxicity monitoring based on the dose-limiting toxicity (DLT) rate. Patients in Arm A and Arm B will be monitored jointly for toxicity. Toxicities will be defined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle on study that meets any of the following criteria:

- CTCAE grade 3 AST (SGOT) or ALT (SGPT) for > 7 days
- CTCAE grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant NCI common terminology criteria that are CTCAE grade ≥3 (except for electrolyte disturbances responsive to correction within 24 h, diarrhea, nausea and vomiting that responds to standard medical care)

An AE must be clinically significant to define DLT e.g. nausea and vomiting < grade 3, alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO3, Mg, Ca, bilirubin) that are grade <3 will not define the DLT.

Monitoring for toxicity will follow a Bayesian-based rule for the probability that the rate of DLT exceeds a maximal tolerated level of 33%. We will assume a Beta (1,2) prior,

which is prior information equivalent to one DLT observed in three treated patients. This minimally informative prior is justified as there is some clinical experience with the investigational therapy. Early termination for toxicity will be considered based on a posterior probability above 75% that the toxicity rate exceeds 33%. Stopping boundaries for toxicity monitoring are provided in the table below.

# Patients (inclusive)	Stop the trial if there are at least this many DLTs total:
1 to 2	Never stop with this many patients
3	2
4 to 6	3
7 to 9	4
10 to 12	5
13 to 15	6
16 to 18	7
19 to 21	8
22 to 24	9
25 to 27	10
28 to 29	11
30	Always stop with this many patient

12.3.2 Evaluation of response:

Only those patients who have measurable disease present at baseline, have received at least two cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

13 Data Reporting / Regulatory Requirements

Adverse event lists, guidelines, and instructions for reporting adverse events can be found in Section 10.

13.1 Data Reporting

Investigative sites are responsible for completing and submitting data using the electronic data capture system.

13.2 Data Collection

13.2.1 Data Collection Forms

Qualified clinical trials study monitors that represent Oncoceutics will complete on-site monitoring. Oncoceutics will be responsible for all data management and statistical analysis.

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

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

1. The Sponsor or designee will conduct an initiation meeting at the study site prior to the start of the study. The study protocol, procedures and CRFs will be reviewed in detail and the study personnel will be trained to carry out the procedures defined in the protocol.
2. The Investigator will be provided with a Study Site Binder for storing study related regulatory and study site documentation; e.g., study logs and forms.
3. All written study documentation entries must be made in blue or black ink. The investigator must review all entries for completeness and accuracy. When changes or corrections are made on any study documentation, the person making the change must draw a single line through the error, then initial and date the correction.
4. Periodic monitoring visits will be conducted on a regular basis by the Sponsor or designee in order to verify the accuracy of data entered on each CRF against the raw data from source documents at the site. Items needing correction/clarification will be identified and brought to the attention of the study site personnel and Principal Investigator, and corrections will be made as appropriate.
5. The CRF will then be sent to the Sponsor or designee for final review and data management. The study database will be validated using appropriate validation processes.
6. The Sponsor or designee may perform a regulatory audit of the study site and may include a complete review of the overall study conduct, regulatory documentation, and selected subject CRFs and source documents.

13.2.2 Patient Consent Form

Informed consent must be obtained before protocol-specified procedures or interventions are carried out. The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records.

The consent form must be approved by the IRB and be acceptable to the Sponsor. Consent forms must be written so as to be understood by the prospective subject. The Informed Consent should be translated and certified into the local language of the respondent, as deemed necessary. Informed consent will be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and by the person who

conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the Sponsor or its designee. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

13.2.3 Site Monitoring

To ensure compliance with current federal regulations and the ICH guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor and duly authorized representative of any entity providing support for this trial. Contractors of the Sponsor will conduct routine monitoring or audit activities for this study. The general scope of such visits would be to inspect study data (regulatory requirements), source documentation and CRF completion in accordance with current FDA Good Clinical Practices (GCP), the ICH guidelines and the respective local and national government regulations and guidelines.

13.2.4 Institutional Review Board Approval

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

The investigator is responsible for keeping their local IRB informed of the progress with study renewal at least once a year. The investigator must also keep the local IRB informed of any significant adverse events, per local institutional guidelines.

Records Retention: FDA regulations (21 CFR 312.62) require clinical investigators to retain all study- related documentation, including source document and CRFs, long enough to allow the sponsor to use the data to support marketing applications. If this study is conducted under an IND, all records must be maintained for:

Two years after the FDA approved the marketing application, or Two years after the FDA disapproves the application for the indication being studied, or Two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

14 PROTOCOL SIGNATURES

SPONSOR PROTOCOL SIGNATURES

Study Title:	A Phase II Study of ONC201 in Recurrent or Metastatic Type II Endometrial Cancer
Study Number:	ONC012
Version:	4
Date:	11 May 2020

This clinical trial protocol was prepared by:

DocuSigned by:
Michael Chiarella
Signer Name: Michael Chiarella
Signing Reason: I am the author of this document
Signing Time: 5/15/2020 | 12:16:19 PM PDT
B9D5E73F5C20462CB84AE2A81D3B4DA2

Signed:_____ Date: 5/15/2020

Michael Chiarella
VP, Clinical Operations
Oncoceutics, Inc.

This clinical trial protocol was reviewed and approved by:

DocuSigned by:
Josh Allen
Signer Name: Josh Allen
Signing Reason: I approve this document
Signing Time: 5/15/2020 | 7:10:28 PM PDT
9645D4DF7BAD4D76A5CDBF85B3CC3D82

Signed:_____ Date: 5/15/2020

Joshua E. Allen, PhD
Chief Scientific Officer
Oncoceutics, Inc.

15 PROTOCOL INVESTIGATOR SIGNATURE PAGE

PROTOCOL INVESTIGATOR SIGNATURE PAGE

Study Title:	A Phase II Study of ONC201 in Recurrent or Metastatic Type II Endometrial Cancer
Study Number:	ONC012
Version:	4
Date:	11 May 2020

I have read this protocol, and I agree that it contains all necessary details for me and my staff to conduct this study as described.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference of Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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