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A Phase 2 Study of Single Agent ONC201 in Recurrent or Metastatic Endometrial Cancer

Supported by: Oncoceutics and Fox Chase Cancer Center

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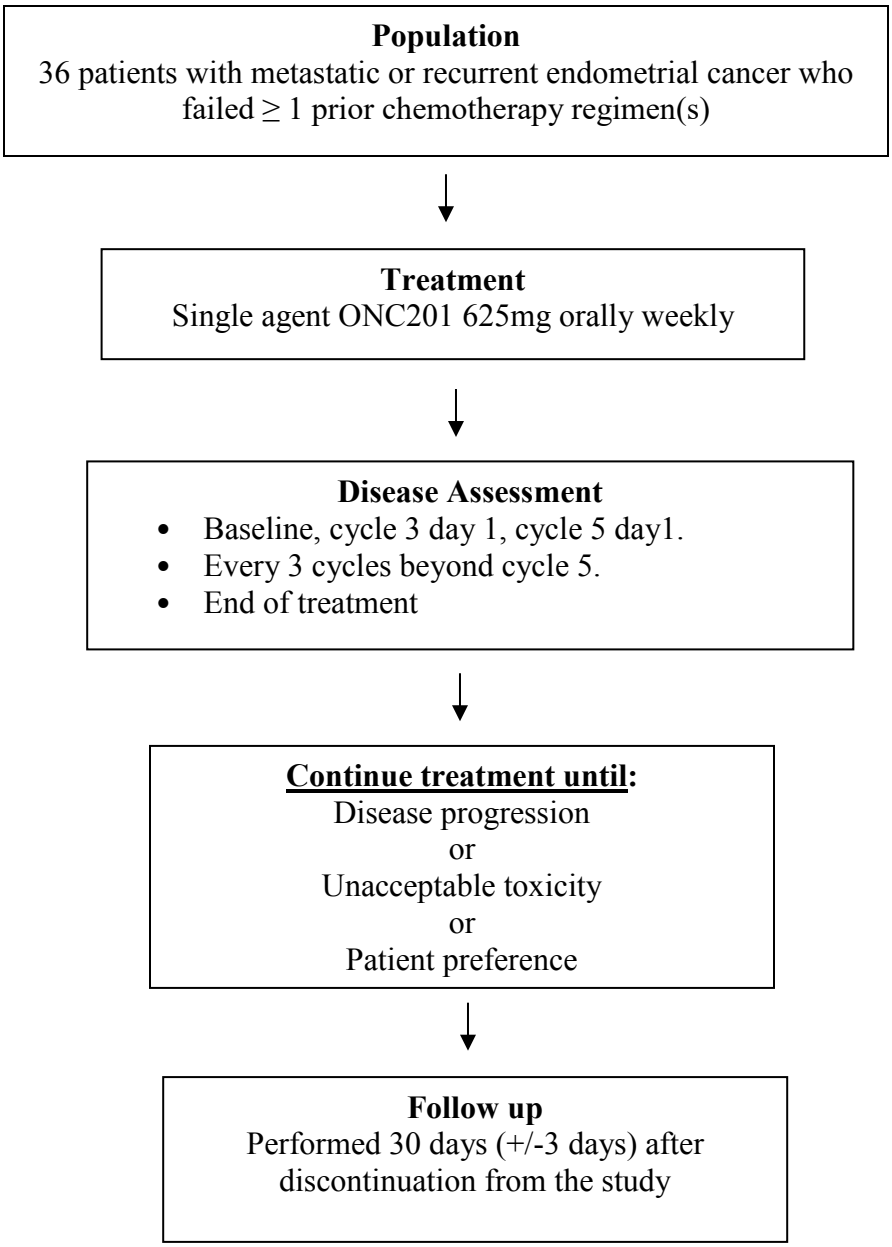
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1.0 Introduction

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.

The type I endometrioid cancers are characterized by alterations in the phosphatidylinositol-3 kinase/serine-threonine kinase/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway; loss of *PTEN* tumor suppressor function or activation of *PIK3CA* are the most common mutations in type I endometrial cancers, leading to overactivation of the PI3K/Akt/mTOR pathway[5]. Other mutations have also been reported in the *KRAS, FGFR2, ARID1A,* and *β-catenin* genes [5, 6]. Microsatellite instability (MSI) is also frequently seen in type 1 tumors [7]. On the other hand, type 2 cancers, in particular those of serous histology, may have alterations in *p53*, *p16, E-cadherin*, *HER2/neu, PIK3CA*, *FBXW7*, and *PPP2R1A* [5, 8].

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 [9]. 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 [9]. Therefore, this

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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 [10]. 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 [11], cisplatin/doxorubicin, and cisplatin/doxorubicin/paclitaxel [12]. Carboplatin/paclitaxel is often used as the first line therapy due to its lower toxicity and equivalent efficacy. Response rates for this regimen range from 40-62% with overall survival ranging 13-29 months [11, 13, 14]. Single agent regimens generate response rates ranging 21-36% for first-line therapy vs. 4-27% when used for second-line therapy [15]; 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 [16]. 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 [17, 18]. 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 [17]. 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 [18]. 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

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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 [19] 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 [20, 21]

The safety profile of ONC201 has been studies in lab animal models and the results are very favorable [22]. 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. This is consistent at early as well as late observation time points, suggesting that the pro-apoptotic signaling in response to ONC201 is a selective effect on tumor cells but not normal cells in a physiological setting (ONC201 – IB).

1.4.1. Clinical safety profile of ONC201

To-date, there have been no deaths attributed to study drug. There have been no SAEs assessed by investigators as "probably" or "definitely" related to study drug, and no discontinuation of ONC201 due to toxicity has been reported. Adverse events that have been observed in previous clinical trials of ONC201 that were attributed by the investigator as possibly-related or probably-related to ONC201 include, but are not limited to fever, nausea, vomiting, fatigue, bone pain, anorexia, weakness, neutropenia, and rash/allergic reaction.

The first-in-human ONC201 clinical trial was an investigator-initiated study, which remains on-going and is being conducted at Rutgers Cancer Institute of New Jersey, titled 'Oral ONC201 in treating patients with advanced solid tumors' (NCT02250781) and 'Continuation of oral ONC201 in Treating patients with advanced solid tumors' (NCT02324621). An accelerated dose escalation design was employed to reduce the number of patients treated at potentially sub-therapeutic doses and to accelerate the determination of the RP2D. A total of 10 evaluable patients (aged 47-80 years) received oral ONC201 once every 3 weeks at 5 dose levels ranging from 125 to 625 mg (125 mg, 250 mg, 375 mg, 500 mg, 625 mg). The study design included one patient per cohort until any patient experienced a Grade 2 adverse event during the first cycle of treatment, defined as 21 days. Enrollment at each subsequent dose level required that all patients enrolled at the prior dose level completed Cycle 1 dosing and were evaluated twenty-one days later to assess safety. No additional patients were needed in the dose-escalation cohort. To further establish the safety profile, another 18 patients were treated at 625mg once every 3 weeks. The design is an open-label, dose-escalation trial of monoagent ONC201 in patients with advanced, refractory tumors who had exhausted or refused standard treatment options for their respective indications

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The primary objective of this study was to determine the recommended Phase II dose (RP2D) of ONC201 administered orally in patients with advanced cancers, as well as to evaluate the safety and tolerability of the drug. Secondary objectives include pharmacokinetics and pharmacodynamics evaluation of ONC201 and preliminary assessment of anti-tumor efficacy.

Seventeen patients have been treated with 625mg ONC201 every 3 weeks in a Phase II trial in recurrent glioblastoma. Other than one instance of Grade 3 neutropenia that was attributed as possibly drug related, none of these patients experienced a possibly or probably related >Grade 2 AE. In the same patient with neutropenia, a non-serious Grade 2 allergic reaction that was probably related to study drug occurred. Two patients with GBM remain on study medication after 14 doses of 625 mg of ONC201, including one patient who continues to exhibit a partial response.

Due to the benign clinical safety profile that was observed with every 3 week dosing, weekly dosing of ONC201 was tested at 375mg and 625mg in Phase I trial in advanced solid tumors. 3 patients received 375mg ONC201 once every week without any reported side-effects. To date 12 patients have received 625mg ONC201 once every week and no drug-related adverse effects have been reported.

In summary, there have been no SAEs assessed by investigators as "probably" or "definitely" related to study drug, and no discontinuation of ONC201 due to toxicity has been reported. The RP2D for ONC201 is 625mg once every week.

1.4.2. Pharmacokinetics

In the pharmacokinetics study ONC201 was found to have a half-life of 11.3 hours in humans. PK analysis was performed in a Phase I dose escalation study in patients with advanced solid tumors. 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. No metabolic or drug-drug interaction have been studied for ONC201 so far (ONC201 IB).

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 induction of the TRAIL pathway [23]. ONC201 also inhibits dopamine receptor 2 (DRD2), resulting in anti-tumor responses in preclinical models [23]. Single agent ONC201 has been examined in open-label Phase I studies in patients with advanced, treatment refractory solid malignancies [23, 24]. Due to its differential anti-

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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 [16].

We hypothesize that single agent ONC201 will demonstrate clinical benefit in women with recurrent or metastatic endometrial cancers, especially in those women with alterations in the PI3K/Akt/mTOR pathway.

1.6. Correlative Testing

Correlative testing will be performed on archival tumor issue 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.

2.0 Objectives

2.1. Primary Objective

Determine the efficacy of single agent ONC201 dosed 625mg orally, once every week in women with metastatic or recurrent endometrial cancer

2.2. Primary Endpoints

1) Progression free survival (PFS) rate at 12 weeks
2) Objective response rate (ORR) via RECIST version 1.1

2.3. Secondary Objectives

1) Evaluation of the safety profile of single agent ONC201 in women with recurrent or metastatic endometrial cancers. Adverse events will be graded using CTCAE v 4.03.
2) To determine the duration of response and duration of stable disease in patients treated with ONC201 dosed 625mg orally, once every week.
3) To determine the median PFS of patients treated with ONC201 dosed 625mg orally, once every week.

2.4. Secondary Endpoints

1) Safety profile of ONC201 will be determined by type, frequency, severity and timing and relationship of Adverse Events and lab abnormalities to ONC201
2) 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.

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3) Median PFS will be calculated as the period between the start of the treatment until disease progression.

3.0 Study Plan

3.1. Description of Study Design, Population and Duration of Study Therapy

We propose a single agent, two stage non-randomized, open label, Phase 2 trial of ONC201 in women with metastatic or recurrent endometrial cancer who failed at least 1 prior chemotherapy regimens. Patients with histologically confirmed endometrial cancer, including but not limited to endometrioid, serous, clear cell, carcinosarcoma, adenosquamous, and mixed histologies, will be eligible. Two patient cohorts will be included: an experimental cohort of endometrioid histology (n=27), and an exploratory cohort consisting of type 2 histologies, including serous, clear cell and carcinosarcoma (n=9). ONC201 will be administered at a dose of 625 mg by mouth weekly until disease progression, unacceptable toxicity, or if the patient discontinues for any other reason. It is anticipated that 36 patients will be enrolled into this study over the course of 18 months. Radiologic tumor assessment would be performed at baseline, 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, will undergo radiologic tumor assessment at the time of discontinuation (End of treatment). If a scan done 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. The confirmatory scan should occur at 12 weeks if disease progression occurred at 6 weeks. Patients who continue treatment beyond progression would undergo another confirmatory scan at the end of 2 more cycles and if the progression is confirmed (RECIST shows >30% PD compared to baseline sum of lesions) they will be come off the study.

4.0 Patient Selection Inclusion & Exclusion

4.1. Inclusion Criteria

4.1.1 Patients must have histologically confirmed metastatic or recurrent endometrial cancer. Eligible histologies include but are not limited to endometrioid, serous, clear cell, carcinosarcoma, adenosquamous, and mixed histologies.

4.1.2 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 11.0

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4.1.3 Must have radiographic disease progression after 1 line of systemic cytotoxic therapy for metastatic disease or with progression within 12 months of completing adjuvant chemotherapy

4.1.4 If available, archived tissue biopsies will be provided for correlative studies

4.1.5 Age $\geq$ 18 years.

4.1.6 ECOG performance status of 0, 1, or 2

4.1.7 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

4.1.8 Prior chemotherapy, hormonal and radiation therapy administered in the adjuvant setting will be allowed.

4.1.9 Life expectancy at least 3 months

4.1.10 Ability to understand and willingness to sign a written informed consent and HIPAA consent document

4.1.11 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.

4.1.12 Patients who are receiving any therapeutic agent for non-neoplastic indication, determined on case by case basis by the principal investigator

4.2. Exclusion Criteria

4.2.1 No prior treatment with ONC201

4.2.2 Patients who have had hormonal therapy, chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered

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more than 4 weeks earlier. Patients who have not recovered to baseline or CTCAE ≤ Grade 1 from related toxicity to all prior therapies. Patients with side-effects CTCAE ≤ Grade 1 due to previous therapy are included. Patients with Non-serious adverse events such as alopecia, fatigue, weakness, loss of appetite and nausea that are non-significant will not be excluded.

4.2.3 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..

4.2.4 The subject is unable to swallow capsules

4.2.5 Patients receiving any other investigational agents

4.2.6 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

4.2.7 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.

4.2.8 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.

4.2.9 Known HIV-positive patients on combination antiretroviral therapy

4.2.10 Known history of HBV or HCV infection.

4.2.11 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.

4.2.12 Pregnant or breast feeding. Refer to section 4.4 for further details.

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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 $\geq$ 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. Subject Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be

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discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email FCCC.MONITOR@fccc.edu or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 Treatment Plan

Patients will be stratified by histology type, consisting of type 1 (endometrioid) and type 2 (for example-serous, clear cell, carcinosarcoma). 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				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
ONC201	625mg	Oral	Weekly	3 weeks

5.1.1. ONC201

During cycle 1, patients will be given ONC201 at the clinic. Beyond cycle 1 ONC201 capsules will be dispensed for every cycle 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 every 7 days (1 week), however if the drug is missed for reasons not related to adverse events +/- 3 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.

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5.2. Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

5.2.1. Drug Interactions

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

5.2.2. 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)

5.2.3. 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.

5.2.4. Other Anticancer or Experimental Drugs

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

5.2.5. 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 disease progression after confirmatory scan
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events (See Table 6.3 of IB for ONC201)
- Patient required > 3 dose reductions
- Patient becomes pregnant
- Patient decides to withdraw from the study

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

5.4. Duration of Follow up

Patients removed from the study for unacceptable toxicity will move into safety follow-up and will be followed-up 30 days (+/-3 days) after discontinuation or until resolution or stabilization of the adverse events, whichever occurs last. If a new anti-cancer therapy is started before the scheduled 30 day follow-up, effort should be made to complete the 30 days follow-up before the new drug administration or at least determine if there are any existing side-effects. After a new investigational agent is administered the safety follow-up may not be done

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 at the treating physician's discretion. If treatment delays exceed 14 days due to treatment related AE, study therapy will be discontinued. The reason for study removal and the date the patient was removed must be documented in the medical record and case report form.

6.0 Dose Modifications

6.1. General Principles

Dose modifications will be made based only on the guidelines described in Section 6.0. Dose reductions are permanent; there are no dose re-escalations. Patients requiring > 3 dose reductions must discontinue protocol treatment. Patients requiring treatment to be held > 14 days for recovery from toxicity must discontinue protocol treatment.

6.2. Dose Level Adjustment Table(s)

Dose adjustments onONC201 should be done according to the following table

Dose level	ONC201
0 (baseline)	625mg/week
-1	500mg/week
-2	375mg/week
-3	250mg/week

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6.3. Specific Toxicities and Modifications

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

ONC201 is contraindicated in patients who exhibit severe (Grade 3 or 4) hypersensitivity reactions to ONC201, its excipients, or related compound.

For treatment-emergent AEs as well as treatment related AE, the dose of ONC201 will generally be held until resolution or lowered. However, preclinical studies suggest that adverse events can be mitigated by dose fractionation to lower C_{max}. Thus grade 2-3 AEs may be reduced or eliminated on subsequent cycle by dose fractionation. Six hour separation of fractionated doses is selected based on the anticipated half-life of ONC201 in man and may be adjusted based on clinical data. As described in table 6.3.1 once a patient has been administered ONC201 by dose fractionation all subsequent administration of ONC201 will be fractionated. In the case where clinician does not suspect AE is treatment related, despite meeting criteria within AE table, dose will not be held.

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6.3.1. Dose Delays, reductions and Interruptions

Adverse Event	Dose Adjustment
Grade 1	• No change in dose
Grade 2[a]	• First Occurrence[c] : Hold until ≤ Grade 1. Resume at same dose level • Second occurrence: Hold until ≤ Grade 1. Resume at one dose level lower • Third Occurrence: Hold until ≤ Grade 1. Resume at one dose level lower with ~ half the number of capsules administered followed by the administration of the other half of the capsules 6-12 hours later[b] • Fourth Occurrence: Hold until ≤ Grade 1. Resume at one dose level lower with ~ half the number of capsules administered followed by the administration of the other half of the capsules 6-12 hours later[b]
Grade 3[a]	• First occurrence: Hold until ≤ Grade 1. Resume at one dose level lower • Second occurrence: Hold until ≤ Grade 1. Resume at one dose level lower with ~ half the number of capsules administered followed by the administration of the other half of the capsules 6-12 hours later[b] • Third Occurrence: Hold until ≤ Grade 1. Resume at one dose level lower with ~ half the number of capsules administered followed by the administration of the other half of the capsules 6-12 hours later[b] • Fourth occurrence: Off protocol therapy
Grade 4	• Off protocol therapy

[a] Patients requiring a delay of >2 weeks due to a treatment-related adverse event must be discontinued from study. Treatment may continue for grade 2 adverse events that are not clinically significant at treating physician's discretion.
[b] Split dosing, if necessary, will be administered no earlier than 6 hours apart and no later than 12 hours apart.
[c] Occurrences will be counted as any reoccurring toxicity of the same grade, or higher.

7.0 Study Agent Information

7.1. ONC201 Formulation, Product identification, Package and Labeling

The ONC201 drug substance is a well characterized small molecule produced as a dihydrochloride salt. ONC201 dihydrochloride is a white to off-white solid, freely soluble in water. ONC201 is supplied as 125mg capsules.

7.1.1. Product description

Each ONC201 capsule contains the equivalent 125mg of anhydrous ONC201 free base (approximately 150mg of dihydrochloride), with or without microcrystalline cellulose as an excipient, filled into hydroxypropyl methylcellulose (HPMC).

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7.1.2. Availability

ONC201 will be supplied by Oncoceutics, Inc.

7.1.3. Storage requirements

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).

7.1.4. Route of administration

Oral

7.2. Drug Ordering, Storage and Handling

Following submission and approval of the required regulatory documents, participation in the study initiation meeting and receipt of the site activation letter from the FCCC ISRU, the initial order may be placed. Drug order forms and ordering procedure will be presented at the site initiation meeting.

7.3. Destruction of Drug

At the time of study closure, the unused and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified. Patient returned study medication may be destroyed on site, as per institutional SOPs after documentation on the drug accountability document. Expired study medication may be destroyed on site, as per institution SOPs, during the study.

7.4. Records to be kept at Site; Dispensing and Accountability

It is the responsibility of the Site Principal Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

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8.0 Correlative /Special Studies

The mechanism of action of ONC201 involves DRD2 antagonism, which results in a number of effects that involve changes in signaling pathways in tumor cells and stimulation of the immune system. Furthermore, the sensitivity of tumor cells to ONC201 has been found to be associated with predictive biomarkers.

Downstream of target engagement in tumor cells, ONC201 causes activation of the integrated stress response and dual inactivation of Akt and ERK, the latter of which leads to TRAIL and DR5 induction that induce tumor cell death. There are a series of proteins that participate in these signaling pathways that are associated with tumor cell response to ONC201 and have been shown to contribute to its activity in preclinical models: ATF4, CHOP, DR5, TRAIL. Immunohistochemical assays for FFPE tumor tissues have been developed for these pharmacodynamic markers. In addition, serum prolactin induction serves as a surrogate biomarker of DRD2 antagonism that can be assessed by ELISA.

DRD2 is expressed on the surface on immune cell, such as NK cells, and its antagonism results in immune cell activation. Activation of NK and CD8+ T cells have been observed in response to ONC201 in preclinical studies and in biopsies taken from ONC201-treated advanced cancer patients. This activation is observed in circulation (among peripheral blood mononuclear cells) as well as in the tumor and is associated with a both an increase in the number of cells as well as their activation (e.g. Granzyme B expression).

In addition to the above pharmacodynamic biomarkers, the expression of DRD2 and DRD5, a D1-like dopamine receptor that oppose DRD2 signaling, in tumor cells are predictive biomarkers. Tumor cells that exhbit a DRD2+DRD5- expression signature are more sensitive to ONC201 in preclinical studies. Furthermore, the same expression signature in archival tumor specimens from the every three week schedule cohort in the recurrent GBM study (ONC006) was associated with a superior progression-free survival and overall survival.

8.1. Immunohistochemistry to test markers of response to ONC201 treatment

Archival tumor tissue samples will be obtained at the time of enrollment for subjects enrolled in this study to assess predictive biomarkers, such as DRD2 and DRD5. A minimum of 15 FFPE tissue slides will be obtained if FFPE archived block is available.

Optional on-treatment tumor biopsies will also be obtained and assessed for, pharmacodynamic biomarkers for ONC201 such as ATF4, CHOP, DR5. If an optional on-treatment biopsy is taken a total of 15 FFPE slides prepared from the on-treatment biopsied specimen..

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8.2. Blood for correlate testing

Blood collected will be used for correlate testing that may include evaluation of prolactin as a marker of DRD2 antagonism, as well as other proteins will be measured in serum as pharmacodynamic markers.

Blood will be collected at the following time points: Cycle 1 Day 1 pre-dose and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8 pre-dose; Cycle 1 Day 15 pre-dose; and pre-dose on Day 1 of every subsequent cycle.

Archival tissue and blood specimen will be handled and processed by Protocol Support Lab (PSL) at Fox Chase Cancer Center according to the directions specified in the lab manual. The samples will be sent to Oncoceutics Central Laboratories for correlative testing.

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9.0 Study Calendar

	Screening [H]	Cycle 1 (21 days)						Cycle 2 (21 days)	Cycle 3 (21 days)	Cycle 4 (21 days)	Cycle 5 (21 days)	Cycle 6 and beyond (21 days)	EOT	Safety Follow-up [J]
		Wk1 (+/-3 days)				Day 8 (+/-3 days)	Day 15 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)		30 days (+/- 3 days)
		Day1	Day2	Day3	Day 4									
Informed Consent and HIPAA [A]	X													
Medical History	X													
Physical Exam	X	X						X	X	X	X	X	X	X
Concurrent Medications	X	X				X	X	X	X	X	X	X	X	X
Performance Status (ECOG)	X	X						X	X	X	X	X		X
Weight	X	X						X	X	X	X	X		X
Height	X													
Vital Signs [B]	X	X				X	X	X	X	X	X	X	X	X
Pregnancy Test [C]	X	X						X	X	X	X	X		
Urine Analysis [D]	X													
12-Lead EKG [N]	X													

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	Screening [H]	Cycle 1 (21 days)						Cycle 2 (21 days)	Cycle 3 (21 days)	Cycle 4 (21 days)	Cycle 5 (21 days)	Cycle 6 and beyond (21 days)	EOT	Safety Follow-up [J]
		Wk1 (+/-3 days)				Day 8 (+/-3 days)	Day 15 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)	Day 1 (+/-3 days)		30 days (+/- 3 days)
		Day1	Day2	Day3	Day 4									
CBC w/diff, plts	X	X				X	X	X	X	X	X	X	X	X
Serum Chemistry[E]	X	X				X	X	X	X	X	X	X	X	X
PT/PTT, INR	X													
Archival Tissue [F]	X													
Brain Scan[L]	X													
Radiologic Tumor Assessment [K]	X								X		X	X[K]	X [M]	
AE Assessment	X	X				X	X	X	X	X	X	X	X	X
ONC201 [G]		X				X	X							
Blood for correlate testing [I]		X	X	X	X	X	X	X	X	X	X	X	X	X
CA-125 [O]	X	X						X	X	X	X	X	X	X
Tumor Biopsy [P]						X								

Footnotes

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A. Informed consent must be signed within 30 days of registration. If signature is outside that window the patient must sign a new consent
B. Temperature, Pulse, Respiratory rate, Blood Pressure
C. For WOCBP only and must be done within 72 hours of receiving first dose and D1 each cycle
D. Color and appearance, pH and specific gravity, bilirubin, glucose, ketones, leukocytes, Nitrite, Occult blood, Protein, Urobilinogen. This test will be done at baseline at the discretion of the treating physician.
E. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.
F. If available, 15 slides for IHC, and H&E
G. Onc201 will be administered at clinic during the first cycle. Beginning cycle 2 ONC201 will be dispensed to patients to be taken at home. ONC201 dosing is once every 7 days. If a dose is missed for reasons other than toxicity, patients have a window of +/- 3 days to take the drug.
H. Must be done within 28 days of C1D1
I. Blood (for serum and plasma) will be collected at: baseline and 2 hours, 24 hours, 48 hours, and 72 hours after the first dose of ONC201; Cycle 1 Day 8; Cycle 1 Day 15; pre-dose on day 1 of every subsequent cycle. Blood will also be collected at the end of treatment visit and 30 day follow up visit.
J. 30 days after End of Treatment (EOT)
K. Pelvis and abdomen scans should be performed and other scans can be done at Physician's discretion. After baseline CT, patients will undergo tumor screening on C3D1, C5D1 Beyond cycle 5, radiologic assessments should be done at the end of every 3 cycles i.e. C8D1, C11D1, etc and thereafter at EOT.
L. Only for patients with known history of brain metastasis at baseline. Previous scan done within 30 days will be acceptable. More brain scans during the trial will be done at the treating Physician's discretion.
M. At treating Physician's discretion. Scan done within last 30 days will be acceptable
N. As clinically indicated
O. Only at Physician's discretion. Can be collected at other time-points during the study at physician's discretion.
P. Optional tumor biopsy: Biopsy can be done at least 24 hours after the second administration of ONC201. This biopsy will be performed if deemed standard of care.

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10.0 Adverse Events

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.

10.1.1. Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

10.1.2. Attribution/Relationship to study drug

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

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10.1.3. Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts, or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.

10.2. Recording and Reporting Responsibilities

10.2.1. Investigative Site Recording Responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All reportable SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the Sponsor should the event require further investigation.

10.2.2. Investigative Site Reporting Responsibilities:

1. The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the sponsor within 24 hours of becoming aware of the event. All subsequent SAEs must be reported for up to 30 days after the last treatment.

   Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent by email to

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SAE.FCCC@fccc.edu.

2. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval **prior** to submission to the IRB.

3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor-Investigator

4. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

5. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

Participating sites should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

10.2.3. Sponsor Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
    a. Unexpected (in terms of nature, severity, or frequency) given
        i. (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
        ii. (b) the characteristics of the subject population being studied;
    b. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
    c. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

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2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.
3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at OCR.
4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

Food and Drug Administration:
Telephone 1-800-FDA-1088
Fax 1-332-FDA-0178
http://www.fda.gov/medwatch/report.htm

10.3. 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 the Fox Chase Cancer Center Study Monitor who will notify Dr. Mantia-Smaldone and Oncoceutics.

11.0 Measures of Effect

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 (RECIST shows >30% PD compared to baseline), they will be come off the study. The confirmatory scan should occur at 12 weeks if the patient shows disease progression at 6 weeks.

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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 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.

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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

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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)

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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.

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For 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.

12.0 Statistical Considerations

12.1. Study Design/Endpoints

For the main cohort (endometrioid histology), a modified Simon two-stage design is planned with a maximum accrual of patients to discriminate between co-primary endpoints of objective response rates of 30% vs. 10% and 12-week progression-free-survival (PFS) rates of 55% vs. 30% (corresponding to median PFS of 3.4 vs. 1.7 months). Stage I has a planned accrual of 13 endometrioid patients. An interim analysis for futility will be performed when the 13 first-stage patients are evaluable for progression at 12-weeks. If ≤ 1 objective response (CR or PR) by RECIST v1.1 criteria (no more than 7%), and ≤ 4 instances of 12-week PFS (no more than 31%), are observed among the initial 13 patients, the endometrioid cohort will be terminated for futility. Otherwise, if >1 patients have demonstrated response or >4 patients are progression free at 12 weeks, the study will proceed to Stage II accrual for a total

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accrual of 27 patients. If at least 6 objective responses (at least 22%), or at least 13 instances of 12-week PFS (at least 48%) are observed among the 27 patients, this agent would be considered worthy of further testing. This design has 8% type-I error, and >80% power to declare success if either alternative hypothesis (high response rate or high PFS rate) are true.

Note that after the 13 first-stage patients have been treated, second-stage patients may be enrolled while the remaining first stage-patients are followed for response and 12 week progression status (to avoid disruptions in recruitment). Enrollment of second-stage patients will stop if it becomes impossible to satisfy the futility rule of >1 objective response or >4 patients being progression free at 12 weeks (e.g. if response criteria were not met and 1 patient still <12 weeks from treatment, but only 3 instances of 12-week PFS have been observed, then further enrollment would stop). Further, patients who may have evidence of early disease progression at 6 weeks (end of cycle 2) may continue on treatment for an additional 6 weeks (2 cycles) in order to confirm true disease progression vs. pseudo-progression. However, any patients who are not evaluated for response or 12-week progression will be considered negative for that outcome (coded as non-responders/progressed at 12 weeks).

The exploratory cohort of up to 9 patients with other histologies (serous, clear cell, or carcinosarcoma) will not undergo formal hypothesis testing. Objective response rate and 12-week PFS rates will be summarized by histology. Accrual to this exploratory cohort may continue if the endometrioid cohort is halted for futility, although no more than 9 non-endometrioid patients will be accrued in total.

12.2. Sample Size/Accrual Rate

In the endometrioid histology cohort 13-27 subjects will be enrolled. In the other histologies cohort (exploratory cohort), 9 subjects will be enrolled. Accrual rate for this trial is estimated to be 1 per month over an 18 month period.

12.3. Analysis of Secondary/Exploratory Endpoints

All patients enrolled in the study and receiving 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.

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- 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 standard descriptive statistics (medians, means, ranges) 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. PFS curves will be calculated separately in the endometrioid histology group and combined "other" histology group. Patients who are lost to follow-up (who withdraw from the study prior to evidence of progression or death) will be considered censored.

12.4. Reporting and Exclusions

12.4.1. Evaluation of toxicity:

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

The study will halt for excess toxicity if the rate of grade 4 toxicities (despite maximum supportive care) is greater than or equal to 25%. Toxicity rates for all histologies will be combined and analyzed together. The study will be terminated early if ever 5 of the first 18 patients accrued (of any histology) have grade 4 or higher toxicity despite maximum supportive care. If the endometrioid cohort proceeds to stage II (total enrollment = 36 patients), and if at any point 9 patients have grade 4 or higher toxicity the study will be terminated. If the endometrioid cohort does not proceed to stage II (total enrollment = 22), and if at any point 6 patients have grade 4 or higher toxicity the study will be terminated. Properties of the stopping rule and final decision rule are tabulated below.

Table 1 - Operating characteristics of toxicity stopping rules							
True toxicity rate	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**
Prob early stop	0.03	0.12	0.28	0.48	0.67	0.81	0.91
Prob declare toxic (final N=36)	0.03	0.15	0.39	0.65	0.84	0.95	0.99
Prob declare toxic (final N=22)	0.03	0.14	0.33	0.55	0.74	0.87	0.94

12.4.2. Evaluation of 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. 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,

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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.

13.0 Data and Safety Monitoring Plan

13.1. Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor-Investigator who will review the data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor-Investigator as applicable.

13.2. Data & Safety Monitoring Board

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed by the Fox Chase Cancer Center Data & Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the Sponsor-Investigator. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data & Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

14.0 Administrative

This study will be conducted in accordance with local, state and Federal regulations and according to accepted good clinical practice guidelines.

14.1. Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit

The ISRU is responsible for compiling and submitting data to the Sponsor-Investigator and statistician on an ongoing basis for monitoring as described in the DSMP and reporting to the Data and Safety Monitoring Board.

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All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

14.2. Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

14.3. Study Agents

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

14.4. Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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15.0 References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.
2. Lajer, H., et al., *Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey.* Acta Obstet Gynecol Scand, 2012. **91**(8): p. 976-82.
3. Ueda, S.M., et al., *Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths.* Am J Obstet Gynecol, 2008. **198**(2): p. 218 e1-6.
4. Bokhman, J.V., *Two pathogenetic types of endometrial carcinoma.* Gynecol Oncol, 1983. **15**(1): p. 10-7.
5. Hecht, J.L. and G.L. Mutter, *Molecular and pathologic aspects of endometrial carcinogenesis.* J Clin Oncol, 2006. **24**(29): p. 4783-91.
6. Byron, S.A., et al., *FGFR2 point mutations in 466 endometrioid endometrial tumors: relationship with MSI, KRAS, PIK3CA, CTNNB1 mutations and clinicopathological features.* PLoS One, 2012. **7**(2): p. e30801.
7. Zighelboim, I., et al., *Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type.* J Clin Oncol, 2007. **25**(15): p. 2042-8.
8. Kuhn, E., et al., *Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses.* J Natl Cancer Inst, 2012. **104**(19): p. 1503-13.
9. Cancer Genome Atlas Research, N., et al., *Integrated genomic characterization of endometrial carcinoma.* Nature, 2013. **497**(7447): p. 67-73.
10. Pecorelli, S., *Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium.* Int J Gynaecol Obstet, 2009. **105**(2): p. 103-4.
11. Miller D, F.V., Fleming G, et al., *Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract].* Gynecol Oncol, 2010. **125**: p. 771.
12. Homesley, H.D., et al., *A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study.* Gynecol Oncol, 2009. **112**(3): p. 543-52.
13. Pectasides, D., et al., *Carboplatin and paclitaxel in advanced or metastatic endometrial cancer.* Gynecol Oncol, 2008. **109**(2): p. 250-4.
14. Sorbe, B., et al., *Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up.* Int J Gynecol Cancer, 2008. **18**(4): p. 803-8.
15. Moxley, K.M. and D.S. McMeekin, *Endometrial carcinoma: a review of chemotherapy, drug resistance, and the search for new agents.* Oncologist, 2010. **15**(10): p. 1026-33.
16. Aghajanian, C., et al., *Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study.* J Clin Oncol, 2011. **29**(16): p. 2259-65.
17. Oza, A.M., et al., *Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group.* J Clin Oncol, 2011. **29**(24): p. 3278-85.

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18. Slomovitz, B.M., et al., *A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma.* Cancer, 2010. **116**(23): p. 5415-9.
19. Allen, J.E., et al., *Genetic and Pharmacological Screens Converge in Identifying FLIP, BCL2, and IAP Proteins as Key Regulators of Sensitivity to the TRAIL-Inducing Anticancer Agent ONC201/TIC10.* Cancer Res, 2015. **75**(8): p. 1668-74.
20. Ishizawa, J., et al., *ATF4 induction through an atypical integrated stress response to ONC201 triggers p53-independent apoptosis in hematological malignancies.* Sci Signal, 2016. **9**(415): p. ra17.
21. Kline, C.L., et al., *ONC201 kills solid tumor cells by triggering an integrated stress response dependent on ATF4 activation by specific eIF2alpha kinases.* Sci Signal, 2016. **9**(415): p. ra18.
22. Allen, J.E., R.N. Crowder, and W.S. El-Deiry, *First-In-Class Small Molecule ONC201 Induces DR5 and Cell Death in Tumor but Not Normal Cells to Provide a Wide Therapeutic Index as an Anti-Cancer Agent.* PLoS One, 2015. **10**(11): p. e0143082.
23. Allen, J.E., et al., *Discovery and clinical introduction of first-in-class imipridone ONC201.* Oncotarget, 2016.
24. Stein MN, M.T., Moss RA, Silk AW, Chan N, Haffty BG, DiPaola RS, Beckett Y, Bentlyewski E, Zheng L, Fang B, Allen JE, Mehnert JM. , *First-in-human dose escalation study of oral ONC201 in advanced solid tumors.* J Clin Oncol, 2015. **33**.

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