A Phase II Trial of Enzalutamide in Patients with Androgen Receptor Positive (AR+) Ovarian, Primary Peritoneal or Fallopian Tube Cancer and One, Two or Three Prior Therapies.

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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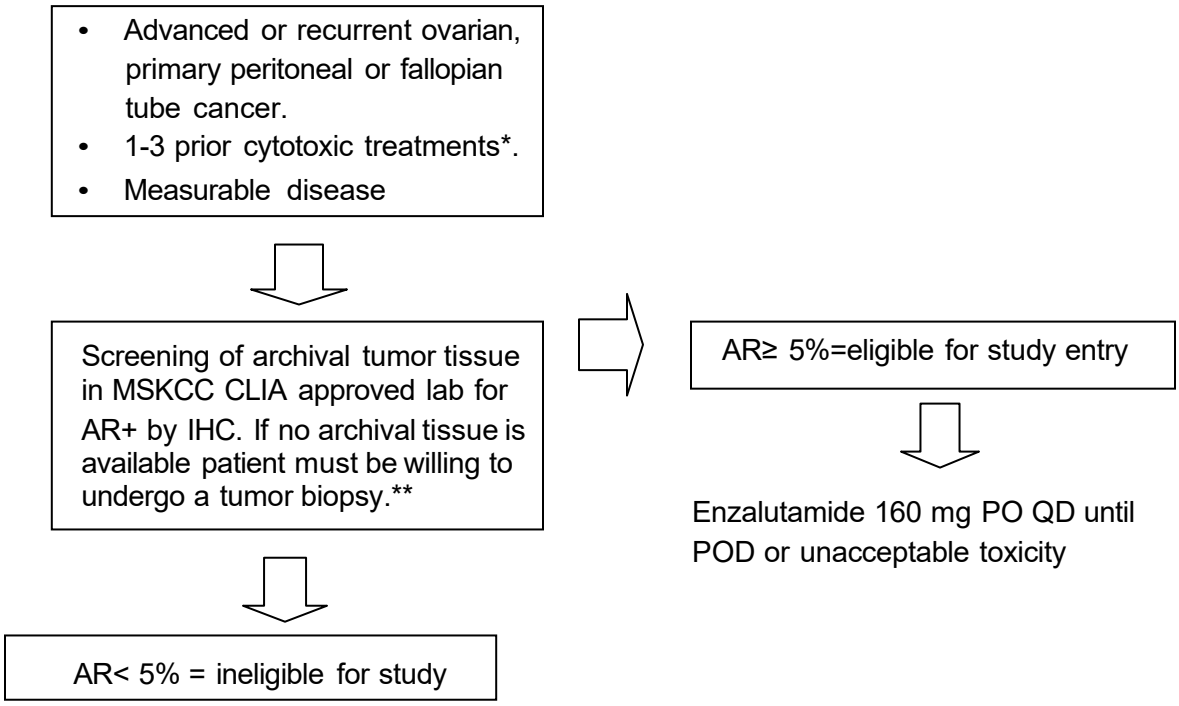
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II, single-institution, open-label trial of enzalutamide 160 mg PO QD in patients with androgen receptor (AR)+ ovarian, fallopian tube or primary peritoneal cancer with measurable disease and one, two or three prior cytotoxic treatments. All enrolled patients will be treated with enzalutamide 160 mg PO QD until progression of disease (POD), unacceptable toxicity or withdrawal from study. All treatments will be administered in the outpatient setting.



*A maximum of 19 enrolled patients will have 3 prior therapies

** In cases where multiple blocks are available staining will be performed on unstained slides from 3 separate blocks. If ≥ 5% AR tumor staining is seen on ≥ 1 slide the tumor will be considered to be AR+.

2.1 OBJECTIVES AND SCIENTIFIC AIM

Primary Objective:

- To estimate the proportion of women with AR(+) ovarian, primary peritoneal, or fallopian tube cancer who survive progression free for at least 6 months and the proportion of patients who have objective tumor response (complete or partial response) by RECIST 1.1 criteria when treated with enzalutamide 160 mg PO QD.

Secondary Objective:

- To determine the frequency and severity of adverse events as assessed by NCI CTCAE version 4.0 in women with AR (+) ovarian, primary peritoneal, or fallopian tube cancer treated with enzalutamide 160 mg PO daily.

Exploratory Objective:

- To perform optional tumor biopsies following treatment with enzalutamide, in order to determine the effect of treatment with enzalutamide on androgen receptor expression
- To observe the effect of enzalutamide on serum testosterone and estradiol levels in women with AR+ ovarian, primary peritoneal, or fallopian tube cancer.

3.0 BACKGROUND AND RATIONALE

3.1 Androgen Receptor and Ovarian Cancer

Ovarian cancer is the second most common gynecologic malignancy and the leading cause of death among women with gynecologic malignancies. There are an estimated 21,990 new cases and 15,460 cancer-related deaths from ovarian cancer in the United States annually [1]. Approximately 75% of women with epithelial ovarian cancer present with advanced (stage III or IV) disease. Standard treatment for women presenting with advanced ovarian cancer includes cytoreductive surgery followed by combination chemotherapy with platinum and taxane agents [2]. The majority of these women will recur and be treated with multiple lines of single-agent cytotoxic chemotherapy. Progression-free survival following first, second and third remission are 10.2, 6.4 and 5.6 months respectively[3]. Long-term survival among women diagnosed with advanced-stage ovarian cancer remains < 30%. Additional options for recurrent and persistent disease are clearly needed [4, 5].

Androgen receptors (ARs) are found in 67-90% of cases of epithelial ovarian cancer, and are more prevalent than estrogen (32-55% of cases) or progesterone receptors (46-52% of cases) in this disease [6-10]. Historically, studies targeting androgen inhibition in ovarian cancer using GnRH agonists or AR antagonists have shown a response rate of 0-22% and stable disease in 8-70% of women [11-20]. Our group at MSKCC published a negative phase II study of goserelin and bicalutamide consolidation therapy in patients with 2 or more prior therapies in 2007; androgen inhibition in ovarian cancer has largely been ignored since that time [21].

However, all clinical studies of androgen inhibition in ovarian cancer to date have been performed in an unselected population of patients with multiple lines of prior treatment. Recent preclinical data shows that primary cultures of AR+ ovarian cancer cells show an increase in cell division when exposed to androgen, and that this activity is reversed when androgen in inhibited[22]. In addition, androgen receptor positivity has been shown to decrease following chemotherapy, indicating that patients with multiple lines of prior treatment may be less likely to be AR+ and therefore less likely to respond to antiandrogen therapy.

3.2 Enzalutamide

Enzalutamide is a novel small molecule androgen-receptor antagonist selected for its activity against cells overexpressing the androgen receptor [23]. Enzalutamide has a novel mechanism of action that is unlike that of bicalutamide and has been shown in preclinical studies to provide a more complete suppression of the antiandrogen receptor pathway than bicalutamide. Enzalutamide slows growth and induces cell death in AR expressing cells via three complementary actions. Enzalutamide blocks testosterone binding to the androgen receptor, impedes nuclear translocation of the androgen receptor, and inhibits binding of DNA. Preclinical data have demonstrated that enzalutamide is superior to bicalutamide in each of these three actions.

In a mouse xenograft model of prostate cancer using an androgen receptor overexpressing cell line, Enzalutamide treatment resulted in a dose-dependent reduction in tumor volume ($p<0.05$ and $p<0.01$ for mid-and high-dose groups vs. vehicle, respectively). Enzalutamide treatment resulted in unmeasurable tumors in 1/7 animals in the low-dose group and 3/7 animals in the high-dose group. As expected, bicalutamide had little effect on tumor growth.

Enzalutamide binds with high affinity to the human androgen receptor (K_i= 13 nM). Other targets for which measurable enzalutamide binding was detected included the human progesterone receptor with a 50% inhibitory concentration (IC_{50}) of 10-25 μM and the rat gamma amino butyric acid-gated chloride channel (IC_{50}= 2.6 μM; K_i=2.1 μM [1.0 μg/mL]). No significant binding was detected with the remaining 70 receptors.

3.3 Previous Human Experience with Enzalutamide

The safety and tolerability of enzalutamide have been evaluated in numerous clinical studies in both healthy adult male volunteers and in male patients with prostate cancer. The duration of exposure ranges from a single dose to more than 4 years. The estimated safety, PK, and tolerability are based primarily upon the data collected from the completed Phase 1-2 study (S-3100-1-01).

Study S-3100-1-01 was an open label, dose-escalation study of enzalutamide in 140 patients with advanced prostate cancer. Patients were treated with enzalutamide at doses of 30 to 600mg/day until disease progression or intolerable side effects developed.

In this study, enzalutamide was absorbed rapidly after oral administration, with the median time to C_{max} after a single dose occurring at 1 hour (range 0.42 to 4 hours postdose). No major deviations from dose proportionality were observed over the dose range of 30 to 600mg. Due to the long $t_{1/2}$ (~5.8 days), it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulated approximately 8.33-fold relative to a single dose. The peak-to-trough ratio was approximately 1.25, indicating that the average difference between the peak and trough concentrations was ≤ 25%. As a result of the low daily fluctuations, plasma profiles at steady-state resembled a constant infusion. The trough values in individual patients remained constant beyond Day 28 of chronic therapy, suggesting time-linear PKs once steady state was achieved.

Grade 3/4 adverse events reported by at least 3% of patients were fatigue (14%), anemia (4%), and back pain (3%). Fatigue was the most frequently reported adverse event, with dose-dependent increases of Grade 3 fatigue (0% at 150mg/day, 9% at 240 mg/day, 15% at 360mg/day and 20% at 480 mg/day). At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue (1 of 29 patients [3%] who received 240mg/day, 3 of 28 patients [11%] who received 360mg/day and 5 of 22 patients [23%] who received 480mg/day, compared with 0 of 59 patients who received 30, 60 or 150 mg/day). After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with prostate-specific antigen (PSA) rise. The dose of 240mg/day was defined as the maximum tolerated dose.

At the highest dose of 600mg/day, 2 of 3 patients had dose-limiting toxicities (DLT) (seizure, rash, respectively), both of which led to treatment discontinuation. Other causes of treatment discontinuation included rash (n=1 at 480 mg/day), and a myocardial infarction after 15 weeks of 360mg/day in a patient with a history of diabetes, hypertension, and hypercholesterolemia. One witnessed seizure at 360 mg/day and a possible seizure at 480 mg/day were also reported. No deaths and no other drug-related serious adverse events were reported.

3.3 Enzalutamide and Prostate Cancer

The AFFIRM trial, a randomized, double-blind, placebo-controlled, phase III trial, evaluated whether enzalutamide could prolong overall survival in men with castration resistant prostate cancer who progressed following docetaxel-based chemotherapy. Patients who had previously received ≤ 2 regimens of docetaxel-based chemotherapy were randomized 2:1 to enzalutamide 160mg PO QD or placebo. Treatment with corticosteroids was allowed but not required. Between September 2009 and November 2010 1,199 patients were randomized. Based on a planned interim analysis at 520 death events, the Independent Data Monitoring Committee recommended the study be unblinded and placebo patients offered MDV3100 due to a significant OS benefit ($p<0.0001$; HR 0.631) . The estimated mean OS was 18.4 months for MDV3100 treated patients compared to 13.6 months for placebo treated men, a median OS difference of 4.8 months[24].

The most common (≥5%) grade 1-4 adverse reactions included asthenia or fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3-4 adverse reactions were reported in 47% of patients treated with enzalutamide and in 53% of those on placebo.

Enzalutamide was subsequently FDA approved on August 31, 2012 for treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

3.4 Androgen Inhibition and Breast Cancer

The AR is expressed in 60-80% of breast cancers and has been implicated in breast cancer biology [25]. High androgen levels are associated with an increased risk of developing breast cancer in postmenopausal women and androgens have been shown to initiate tumor formation via the AR in animal models [26, 27].

A study evaluating the effects of leuprorelin acetate in women with breast cancer demonstrated responses (complete or partial) predominantly in premenopausal women [28]. In this study, hormone receptor status was unknown on any of the postmenopausal patients. The majority of premenopausal patients had ER + disease. Hot-flashes and weight gain were the only reported toxicities.

In another study, goserelin was administered to 118 pre-/peri-menopausal women of varying ER status. With the exception of hot-flashes, the therapy was well tolerated. The overall response rate was 45% and median time to progression was 59 weeks [29].

Abiraterone acetate is a steroidal inhibitor of CYP17 that blocks two important enzymatic activities in the synthesis of testosterone. A phase I study of abiraterone acetate in estrogen receptor (ER) positive or AR positive advanced breast cancer patients has been completed. A total of 25 patients were treated in 6 patient cohorts at doses between 250mg and 2000mg PO daily. At the 1000mg and 2000mg dose levels good suppression of estradiol, testosterone, DHEA and DHEAS were seen. Two patients (both ER+/AR+) were previously treated with multiple lines of hormonal therapy but continued on treatment with abiraterone acetate for > 11 months. One of these patients achieved a radiographic partial response. It was concluded that abiraterone acetate is well tolerated in advanced breast cancer patients with preliminary evidence of anti-tumor activity at the 1000mg dose level [30].

3.5 Rationale for Current Study

In summary, recent data shows that AR+ primary cultures of ovarian cancer cells proliferate in the presence of androgen and this proliferation is reversed by androgen inhibition. AR expression may be decreased following exposure to multiple lines of cytotoxic chemotherapy. Abiraterone acetate has shown promising results in patients with

AR+ breast cancer; however due to suppression of adrenally produced androgen it can produce severe side effects related to hypokalemia, hypertension and edema. In the ovarian cancer population, where malignant ascites is common, toxicities related to increased edema from abiraterone and prednisone would be significant.

Prior targeted therapies for treatment of ovarian cancer have shown response rates of 0%-21% and PFS at 6 months of 6.5%-40.3% in patients with recurrent or advanced ovarian cancer and a history of 1-2 prior cytotoxic therapies (Table 1).

Table 1.

Study	Agent	Target	N	Response Rate	PFS at 6 Months
170-C	Gefitinib	EGFR	27	3.7%	14.8%
170-D	Bevacizumab	VEGFA	62	21%	40.3%
170-E	Imatinib	Bcr-abl/c-kit/PDGFR	56	1.8%	16.1%
170-F	Sorafenib	VEGFR/PDGRR/RAF	59	3.4%	23.7%
170-G	Lapatinib	EGRR/HER2neu	26	0.0%	7.7%
170-H	Vorinostat	HDAC	27	3.7%	7.4%
170-J	Enzastaurin	PKC-beta	27	7.4%	11.1%
170-K	Mifepristone	PR	22	4.5%	13.6%
170-M	Dasatinib	Scr/bcl-abl/c-kit	34	0%	20.6%
170-N	A6	uPAR	31	0%	20.6%
170-P	AMG-102	HGF(c-met)	Suspended after first stage		

Earlier studies examining alternative methods of androgen inhibition in ovarian, primary peritoneal, and fallopian tube cancer have all been performed in an unselected population of women, typically with multiple prior lines of therapy. Drawing on recent advances, the present study will be performed in a selected population of women with AR+ advanced ovarian, primary peritoneal, or fallopian tube cancer (≥5% by IHC) with measurable disease. Enrolled patients will have had only one, two or three prior cytotoxic therapies. All enrolled patients will be treated with enzalutamide 160 mg PO QD until progression of disease (POD), unacceptable toxicity or withdrawal from study. Based on the prior response rates that have been seen with targeted therapy of recurrent or advanced ovarian cancer (Table 1), and the relatively benign side effect profile of enzalutamide, we will consider this treatment worthy of further study if there is an observed response rate of 12.5% or an observed 6 month PFS interval is seen in 22.5% of patients. Given that enzalutamide 160 mg PO has not previously been administered to women with ovarian cancer this study will utilize a safety lead-in. If ≥ 5 out of the first 15 patients develop a DLTduring the first 28 days of treatment then the study will be put on hold. If this does not occur then enrollment will continue.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single-institution, single-arm, open-label, phase II study of enzalutamide 160mg by mouth once daily in patients with AR+ recurrent or advanced ovarian, primary peritoneal or fallopian tube cancer. After signing a screening consent, patients archival tissue will be evaluated for degree of AR positivity by AR staining. Patients with no archival tissue available will undergo a biopsy (using the modality deemed most appropriate by the patient's physician) for collection of tumor tissue for AR positivity by IHC. Only AR+ patients, defined as ≥5% positivity by IHC, will be included. All IHC testing will be performed in the MSKCC Clinical CLIA approved laboratory.

All eligible patients will have measurable disease by RECIST 1.1 criteria and will have received one, two or three prior cytotoxic treatments for their disease. A maximum of 19 enrolled patients will have 3 prior therapies. Patients will be treated until POD, intolerable toxicity or withdrawal of consent.

The primary endpoint of this trial is to determine the proportion of women with AR(+) ovarian, primary peritoneal, or fallopian tube cancer who survive progression free for at least 6 months and the proportion of patients who have objective tumor response (complete or partial response) by RECIST 1.1 criteria when treated with enzalutamide 160mg PO QD.

The frequency and severity of adverse events as assessed by NCI CTCAE version 4.0 will be described. Optional tumor biopsies will be performed at end of treatment, in order to explore the effect of enzalutamide on tumor AR expression.

4.3 Intervention

Prior to initiation of treatment patients will sign a screening informed consent form for AR IHC testing. If archival tissue is not available then the patient must consent to a biopsy. In cases where multiple blocks are available staining will be performed on unstained slides from 3 separate blocks. If ≥ 5% AR tumor staining is seen on ≥ 1 slide the tumor will be considered to be AR+. Only those patients found to have ≥5% AR by IHC will be eligible for treatment.

All enrolled patients will be treated with enzalutamide 160mg PO QD. Study drugs will be self-administered by patients. A cycle is 28 days. Patients will be required to maintain a pill diary to record each dose of drug taken (see **Appendix A**). All toxicities will be graded using CTCAE version 4.0. Toxicities will be evaluated during physician assessments performed every 2 weeks during the first cycle and every 4 weeks during subsequent cycles of treatment with enzalutamide.

Patients will continue to receive study treatment until POD (as defined by RECIST 1.1), unacceptable toxicity or withdrawal of consent.

Dose modifications will be allowed as described in **Section 9.**

Enrollment will proceed following a safety lead-in of 15 patients. If ≥ 5 patients develop any of the following events classified as dose-limiting toxicity (DLT) during the **first 28 days** of treatment the study will be halted and the PI will examine the toxicity profile and determine whether lower doses will be added. DLT is defined as:

- Any event consistent with a seizure of any grade
- Grade ≥ 3 diarrhea, nausea, or vomiting that does not improve to Grade 1 within 14 days of initiating standard of care therapy
- Grade ≥ 3 decreased platelet count with associated bleeding
- Grade ≥ 3 absolute neutrophil count (ANC) that persists for 7 or more days or that is associated with fevers (febrile neutropenia)
- Any other ≥ Grade 3 non-hematologic toxicity determined to be related to study drug

If < 5 patients develop one of the above events during the first 28 days of treatment then enrollment will proceed following a two-stage design. A total of 28 patients (including the first 15) will be enrolled during the first stage. If 3 or more patients have clinical response or 5 or more patients have no progression/death at 6 months, then the study will open to the second stage of accrual. No more than 9 out of the 28 patients (1/3) enrolled during stage I will have 3 prior therapies. In stage II, an additional 30 patients will be enrolled. At the end of stage II, if at least 7 of 59 (28+30=58) patients have clinical response or at least 13 of 59 patients survive progression free for 6 months, this will be considered as a positive trial.

Patients will be evaluated for radiographic response every 2 cycles (8 weeks) and at the end of study. Response is defined as the best over-all response achieved by RECIST 1.1 criteria while on study treatment.

At end of treatment an optional tumor biopsy will be performed in patients who consent to this procedure.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Enzalutamide

Enzalutamide is a white to off white solid. It is insoluble in water. It is supplied as soft gelatin filled capsules that are filled to contain 40 mg of active pharmaceutical ingredient.

Each patient will self-administer 160mg (4 capsules) PO daily and should be instructed to take the 4 enzalutamide capsules with a glass of water at approximately the same time each day. Each dose should be recorded in the patient's pill diary. Enzalutamide can be taken with or without food. Patients should not make up missed or vomited doses; patients

should resume dosing at their scheduled time the next day unless otherwise instructed. Patients should not take enzalutamide if more than 12 hours have lapsed since the missed dose.

5.2 Storage and Labeling

Enzalutamide should be stored in a secure location with limited access at 77ºF (25ºC), with excursions permitted to 59ºF to 86ºF (15ºC to 30ºC). Bottles will be labeled with the study protocol number, lot number, contents, directions for use, storage directions, clinical trial statement, and Sponsor (Medivation, Inc.). Patients will be instructed to store study drug at room temperature and out of reach of children.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Advanced or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report
- AR expression ≥5% by IHC. In cases where multiple blocks are available staining will be performed on unstained slides from 3 separate blocks. If ≥ 5% AR tumor staining is seen on ≥ 1 slide the tumor will be considered to be AR+.
- Patients with the following histologic cell types are eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial adenocarcinoma, transitional cell carcinoma, malignant Brenner's tumor, or adenocarcinoma not otherwise specified
- Measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension. Each lesion must be ≥10mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20mm when measured by chest x-ray. Lymph nodes must be ≥ 15mm in short axis when measured by CT or MRI
- Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease
- Patients may have received, but are not required to have received, one or two additional cytotoxic regimens for management of recurrent or persistent disease
- Patients who have received only one prior cytotoxic regimen (platinum-based regimen for management of primary disease), must have a platinum-free interval of less than 12 months, or have progressed during platinum-based therapy, or have persistent disease after a platinum-based therapy
- Patients are allowed to receive, but are not required to receive, non-cytotoxic therapy (such as bevacizumab) as part of their primary treatment regimen. Patients are allowed to receive, but are not required to receive, non-cytotoxic therapy for management of recurrent or persistent disease

- Must be ≥ 18 years of age
- Karnofsky Performance Status (KPS) of ≥ 70%
- Life expectancy of ≥ 12 weeks
- Women of child-bearing potential must have a negative pregnancy test within 14 days prior to commencement of study treatment
- Women of child bearing potential must use an effective form of contraception during study and for at least 6 months after completion of study treatment
- Recovery from effects of recent surgery, radiotherapy, or chemotherapy
    - At least 4 weeks out from their last dose of radiation therapy
    - At least 4 weeks post-op from any major surgical procedure
    - At least 3 weeks out from their last dose of chemotherapy and/or biologic/targeted therapy
- No prior hormonal therapy for treatment of cancer within the past 21 days
- Absence of any psychological, familial, sociological or geographic condition that would potentially hamper compliance with the study protocol
- Prior use of or participation in a clinical trial evaluating and agent that either blocks androgen synthesis (e.g. abiraterone acetate, TAK-700, TAK-683, TAK-448) or targets the AR (e.g., bicalutamide, BMS-641988) (patients who are known to have only received placebo in these studies are eligible)
- Laboratory Test Findings performed within 14 days prior to initiation of study drug showing:
    - Bone marrow function:
        - Absolute neutrophil count (ANC) ≥ 1,000/mcL
        - Platelets ≥ 100,000/mcL
        - Hemoglobin ≥ 8 g/dL
    - Renal function:
        - Creatinine ≤ 1.5 x ULN
    - Hepatic function:
        - Bilirubin ≤ 1.5 x ULN
        - AST and ALT ≤ 2.5 x ULN
- Resolution of all acute toxic effects of prior therapy to NCI CTCAE (Version 4.0) Grade ≤ 1, with the exception of unresolved Grade 2 neuropathy and Grade 2 alopecia, which are allowed
- Patients must be able to swallow tablets whole, without crushing

6.3 Subject Exclusion Criteria

- A history of another invasive malignancy (other than non-melanoma skin cancer or curatively treated in situ carcinoma) with evidence of disease within the past 3 years
- Use of a medication known to lower the seizure threshold within 28 days of first dose of study drug (see **Appendix B** for a representative list of medications known to lower the seizure threshold)
- Known brain metastasis

- History of seizure
- Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95mmHg) despite medical treatment. Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.
- Clinically significant heart disease as evidenced by myocardial infarction or arterial thrombotic event within the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or cardiac ejection fraction measurement of < 50% at baseline
- Refractory nausea and vomiting, requirement for parenteral hydration and/or nutrition, drainage gastrostomy tube, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate study drug absorption
- Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study

7.0 RECRUITMENT PLAN

Patients will be recruited from the patients seen by the Gynecologic Medical Oncology (GMO) Service, Department of Medicine, at Memorial Sloan-Kettering Cancer Center (MSKCC). The investigator will screen patients with ovarian, primary peritoneal and fallopian tube cancer to see if they are eligible for this trial.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment.

8.1 PRETREATMENT EVALUATION

Screening:

- Signature of *screening informed consent*
- Tumor biopsy or paracentesis, if no archival tissue is available
- Verification of ≥5% AR+ by IHC in tumor tissue

To be completed within 30 days prior to start of study drug:

- Signature of *treatment informed consent* following inclusion and exclusion review and determination of patient eligibility for the study
- Physical exam and vital signs (height, weight, pulse, temperature, blood pressure)
- Karnofsky Performance Status (KPS)
- 12-lead ECG
- Baseline radiographic tumor assessment (CT or MRI of abdomen and pelvis; CT of chest) with documentation of sites of disease per RECIST (version 1.1)

To be completed within 14 days prior to start of study drug:

- Pregnancy test in women of child bearing potential
- Blood sampling for:
  - CBC with differential
  - Comprehensive Metabolic Panel (Na, K, Cl, CO2, BUN, CREAT, Ca, Glucose, Bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)

9.1 TREATMENT/INTERVENTION PLAN

Enrolled patients will initiate treatment with enzalutamide 160mg by mouth daily beginning Day 1 of Cycle 1. A Cycle is 28 days. Four 40 mg enzalutamide capsules should be swallowed whole with a glass of water. Enzalutamide should be taken at the same time each day. Missed doses will not be made-up. All doses, and missed doses will be recorded in the patient's pill diary. Patients will remain on treatment with enzalutamide 160mg PO QD (with dosage adjustments as described below) until POD, unacceptable toxicity or withdrawal of consent.

While on study, patients will return for assessments with a treating physician every 2 weeks during the first cycle, and then every 4 weeks. Vital signs, toxicity assessment and blood work will be performed at each start of cycle visit. The pill diary will be collected and a new drug supply and pill diary will be provided. A +/- 4 day window is allowed for each start of cycle assessment.

During screening, every 2 cycles (8 weeks) while on treatment, and at end of study, patients will have a CT or MRI of abdomen and pelvis performed. Best overall response should be confirmed with repeat imaging performed at ≥ 4 weeks. Chest imaging with CT should be performed at baseline. If initial chest imaging is abnormal or continued chest imaging is required to monitor tumor response, then it should be repeated every 2 cycles (8 weeks) while on treatment and at end of study. There is a +/- 7 day window for completion of interval tumor assessments by imaging.

Blood work will be drawn to measure levels of estradiol and testosterone on Day 1 of Cycle 1, Day 1 of Cycle 2, and at end of treatment.

An optional research non-billable tumor biopsy will be performed at end of treatment in consenting patients with accessible disease. A tube of whole blood will be drawn on Day 1 of Cycle 1 and on Day 1 of Cycle 2 for gene expression studies and cell free DNA analysis.

9.2 Overview of Dose Adjustments of Enzalutamide for Toxicity

Report of seizure will result in immediate cessation of enzalutamide. A patient who experiences a DLT (other than seizure) during the safety lead-in phase may be allowed to continue study treatment following adequate recovery and appropriate dose modification. Any dose modification of enzalutamide requires consultation with the study sponsor.

- If Grade 1 or 2 toxicities occur, give supportive care per institutional guidelines. No enzalutamide dose reduction should occur.
- If ≥ Grade 3 toxicities occur that are considered potentially related to enzalutamide, including headache, nausea, vomiting or diarrhea, hold enzalutamide until the toxicity resolves to ≤ Grade 1, unless baseline is grade 2, then until returns to baseline.
- If enzalutamide is held for ≤28 days it may be restarted at the same or a reduced dose at the discretion of the study sponsor (or designee).
- If enzalutamide is held for >28 days the patient should be removed from study treatment

9.3 Drug Interactions

Any medication (see **Appendix B** for representative medications) that may predispose the patient to seizure disorder should be stopped at least 4 weeks prior to starting treatment with enzalutamide.

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect
- Any investigational agent
- AR antagonists
- 5-α reductase inhibitors
- Androgens
- And medication (see Appendix B fro representative medications) that may predispose the patient to seizure

9.4 Precautions Regarding Concomitant Medications

Please refer to the following link for an up to date list of CYP and P-glycoprotein inhibitors, inducers, and substrates.

http://www.fda.gov/Drugs /DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency

9.5 Effects of Enzalutamide on Cytochrome P450 Enzymes and P-Glycoprotein

In vitro studies showed that enzalutamide is an inhibitor of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 that have a narrow therapeutic index (e.g., paclitaxel, phenytoin, warfarin) should be used with caution.

In vitro studies showed that enzalutamide may be an inducer of CYP3A4. Co-administration of enzalutamide with CYP3A4/5 substrates may reduce oral bioavailability and/or accelerate elimination of the CYP3A4/5 substrate.

In vitro studies showed that enzalutamide is an inhibitor of the efflux transporter P-glycoprotein (P-gp). Co-administration of enzalutamide with P-gp substrates may increase the plasma concentrations of the P-gp substrate. Use caution when co-administering P-gp substrates (e.g., digoxin, fexofenadine, paclitaxel) during enzalutamide treatment.

9.6 Drugs That May Increase Enzalutamide Plasma Concentrations

In vitro studies showed that enzalutamide is metabolized by CYP2C8 and CYP3A4/5. Use caution when co-administering a strong CYP2C8 inhibitor (e.g., gemfibrozil) or strong CYP3A4/5 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit juice) during enzalutamide treatment.

9.7 Drugs That May Decrease Enzalutamide Plasma Concentrations

Use caution when co-administering a CYP2C8 inducer (e.g., rifampin) or strong CYP3A4/5 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) during enzalutamide treatment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Screening

		Day 1; Cycle 1	**Day 15; Cycle 1**	**Day 1; Cycle 3, 5, 7… (odd cycles)[7]**	**Day 1; Cycle 2,4,8…(even cycles)[7]**	**End of Study Treatment**
Informed Consent	X					
History & Physical Exam[6]	X	X	X[7]	X[7]	X[7]	X
Toxicity Assessment	X	X	X	X	X	X
Vital Signs	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
KPS	X	X	X	X	X	X
ECG	X[2]					
CT of Chest	X[3]			X[3]		X[3]
Radiographic Tumor Assessment of Abd/Pelvis	X[4]			X[4]		X[4]
CBC with Differential	X	X	X	X	X	X
Pregnancy Test (for patients of child bearing potential)	X					
Comprehensive Metabolic Panel	X	X	X	X	X	X
Liver function Tests	X	X	X	X	X	
Blood for Hormones		X			X[9]	X
Whole blood research test		X[8]			X[8]	
Tumor Biopsy	X[5]					X[5]
Dispense Enzalutamide		X[7]		X[7]	X[7]	

1: Vital signs: blood pressure, heart rate, temperature and weight. Height need only be taken on Cycle 1, Day 1.

2: Hypokalemia should be corrected prior to ECG collection

3: Chest imaging with CT should be performed at baseline. If initial chest imaging is abnormal or continued chest imaging is required to monitor tumor response, then it should be repeated every 2 cycles (8 weeks) while on treatment and at end of study. There is a
+/- 7 day window for completion of interval tumor assessments by imaging.

4: Radiographic tumor assessment of abdomen and pelvis may be performed using CT or MRI. There is a +/- 7 day window for completion of interval tumor assessments by imaging.

5: Patients without adequate archival tissue available will have a biopsy performed. Patients who consent for an end of treatment biopsy will have an optional tumor biopsy performed at end of treatment.

6: Includes recording of concurrent medications and focused physical exam. There is a +/- 4 day window allowable for each start of Cycle assessment.

7: Pill diary and remaining pills should be collected and new pill diary and 1 month supply of study drug should be given to patient.

8: One 10 cc tube of whole blood for gene expression analyses will be collected on Day 1 of Cycle 1 and Day 1 of Cycle 2

9: Blood for hormone levels (testosterone and estradiol) will be collected at start of treatment, Cycle 2, Day 1 and at end of treatment.

10.1 Research Tests

10.1.a Research Bloods

Serum testosterone level and estradiol level will be drawn on Cycle 1, Day 1 of treatment; Cycle 2, Day 1 of treatment, and at end of treatment. These will be collected as research non-billable blood draws. These tests will be performed and reported by the MSKCC central core laboratory. This testing is being performed to observe the effect of enzalutamide on testosterone and estradiol levels in women with ovarian, primary peritoneal, or fallopian tube cancer.

10.1.b Tumor Biopsy

Tumor biopsies will be performed at two time points during this study; a biopsy will be will be performed at screening if no archival tissue is available and an optional biopsy will be performed at end of treatment.

If the patient has archival tissue available that is appropriate for AR IHC staining (block or unstained slides), then archival tissue may be used. In cases where multiple blocks are available staining will be performed on unstained slides from 3 separate blocks. If ≥ 5% AR tumor staining is seen on ≥ 1 slide the tumor will be considered to be AR+.

An optional tumor biopsy will be performed at end of treatment in those patients who have POD, consent to biopsy, and have accessible disease.

Biopsy samples should be fixed in 10% formalin and paraffin embedded. **In cases where a reasonable size biopsy is obtained (i.e., excisional biopsy, 18 gauge needle), such that the pathologist feels there is adequate sample for preparation of both a frozen and fixed specimen, a fresh frozen biopsy should also be collected**. At a minimum, enough tissue should be collected (by FNA or Core) for generation of a FFPE block for H&E and IHC analysis. At a maximum 2 cores should be collected.

Lesions with the greatest change in dimensional size based on interval evaluation are the recommended lesions to be excised. Whenever possible, biopsies at POD should be performed within 3 days of study drug discontinuation.

Biopsies obtained at the time of progressive disease will be used to investigate potential mechanisms of acquired resistance. Biopsy samples will be analyzed for level of AR positivity by IHC in order to determine if the androgen receptor is downregulated during treatment with enzalutamide.

10.2 Correlative Studies

The degree of nuclear AR expression levels will be determined using standard immunohistochemistry methodology on all tissue and reported as percent tumor cells with nuclear AR staining. One-three 5 micrometer superplus frost slides will be used for IHC testing. This testing will be performed at the Memorial Sloan-Kettering Cancer Center CLIA approved Clinical Laboratory using the Dako androgen receptor antibody. Upon receipt of the slide in the clinical laboratory, results will be reported within 48 hours. The relationship between tumor response and degree of AR expression, and/or AR signaling, will be examined. Additional assays for AR signaling, (e.g., gene expression array analyses, mutation analyses, or other immunohistochemistry evaluations) may be performed on remaining tissue to evaluate for molecular phenotypes and patterns associated with activated AR signaling.

Germline DNA will be used both for cell free DNA analysis and as a matched normal for MiSeq analysis. MiSeq will be used to evaluate for alterations within the androgen, estrogen, and progesterone receptors. Germline DNA from peripheral blood will be used to filter out germline variants. The germline DNA sequencing data will be used as a filter to define somatic alterations and will not be reported. A 10cc tube of whole blood will be collected on Cycle 1, Day 1 and on Cycle 2, Day 1 for use in gene expression analyses. This testing will be performed at Memorial Sloan-Kettering Cancer Center.

Archived patient blood and/or tissue may be sent to Medivation Inc. and/or Astellas for additional analyses.

Any additional future studies performed using the clinical information, blood, or tissue collected from this study will only be performed after completion of appropriate institutional approval.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Most Frequent Adverse Events

The safety and tolerability of enzalutamide have been evaluated in 13 studies. It is estimated that a total of 124 healthy volunteers, 16 subjects with hepatic impairment, and approximately 1800 patients with prostate cancer have been exposed to enzalutamide in completed, open-label, and ongoing blinded studies. No study has been terminated early for safety reasons.

Enzalutamide (160 mg daily) was generally well-tolerated in the placebo-controlled CRPC2 study of 1199 patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. The adverse events occurring in at least 5% of the enzalutamide group and at an incidence at least 2% greater than in the placebo group included fatigue (33.6% vs. 29.1%), diarrhea (21.4% vs. 17.5%), hot flush (20.3% vs. 10.3%), musculoskeletal pain (13.6% vs. 10.0%), headache (11.6% v 5.5%), insomnia (8.6% vs. 6.0%), anxiety (6.4% vs. 4.0%), hypertension (6.1% vs. 2.8%), and nasopharyngitis (5.1% vs. 3.0%).

Other adverse events reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the adverse events include: falls (4.0% vs.1.3%), dry skin (3.6% vs. 1.3%), and pruritus (3.5% vs. 1.3%). A possible cognitive effect of enzalutamide was observed with a greater proportion of patients in the enzalutamide-treated group (4.1% vs. 1.8%) reporting the following adverse events: memory impairment, cognitive disorder, amnesia, disturbance of attention, and dementia. In addition, events related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide-treated group (1.6% vs. 0.3%).

During pre-market evaluation, seizure was identified as a risk associated with enzalutamide treatment. In the controlled clinical study, 5 patients (0.6%) experienced a seizure out of 800 patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients treated with placebo. One additional serious adverse event reported by the Investigator as syncope was identified by the Sponsor as having several features suggesting seizure as the most likely diagnosis. Confounding factors may have contributed to the occurrence of seizures in several of these cases. Dose appears to be an important predictor of seizure, with a greater risk of seizure at daily doses higher than 160 mg. In a dose escalation study involving 140 patients, no patients experienced seizures at or below daily doses of 240 mg, whereas 3 seizures were reported, 1 each at 360, 480, and 600 mg/day.

Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medications that may lower the seizure threshold. Enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

11.2 Safety Measurements

Safety and tolerability will be determined by frequent assessment of adverse events, physical examinations, vital signs, and safety laboratory assessments as defined in section 10.1. A safety follow-up visit will be conducted approximately 30 days after the last dose of enzalutamide.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

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.

12.2 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 $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$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 will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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.

12.3 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.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and $\geq$10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional 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), but NOT lung.

Use of MRI remains a complex issue. 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. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, we will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next.

If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Response Criteria

12.41 *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.

12.42 *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).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

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).

12.43 ***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

13.1 CRITERIA FOR REMOVAL FROM STUDY

Study treatment will be discontinued for the following reasons:

- Progression of disease
- Persistent or unacceptable toxicity despite appropriate dose reductions
- Withdrawal of consent
- If in the opinion of the investigator continuation on study poses unreasonable risks to the patient. This might include patients who fail to return for adequate follow-up, hampering the ability to monitor toxicities

Any patient discontinuing study drug should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule. The patient's tumor status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up. All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported and followed to resolution as above. Patients should be contacted at least 30 days after discontinuing study medication to collect and /or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

Any patient, who has not yet shown objective disease progression, should continue to be followed as per RECIST 1.1.

14.1 BIOSTATISTICS

This is a single institution, single-arm unblinded Phase II trial of enzalutamide 160 PO QD in patients with AR (+) ovarian, primary peritoneal, or fallopian tube cancer with measurable disease following 1-3 prior cytotoxic therapies. The primary endpoint includes both the progression free survival (PFS) at 6 months, which detects stabilization of disease, and the best overall response(complete or partial response by RECIST 1.1). If either endpoint indicates efficacy, the treatment will be considered clinically interesting and worthy of further investigation.

14.2 Safety Lead-in

In order to reduce patient risk, we will examine in detail the first cycle DLT and other safety data for the first 15 patients before enrolling the rest of the study's patients. A patient is considered toxicity-free for the purpose of the trial if he/she completes the first cycle of therapy (28 days) without experiencing a DLT as defined as:

- And event consistent with a seizure of any grade
- Grade ≥ 3 diarrhea, nausea, or vomiting that does not improve to Grade 1 within 14 days of initiating standard of care therapy
- Grade ≥ 3 platelet count with associated bleeding
- Grade ≥ 3 absolute neutrophil count (ANC) that persists for 7 or more days or that is associated with fevers (febrile neutropenia)
- Any other ≥ Grade 3 non-hematologic toxicity determined to be related to study drug

If a patient experiences a DLT during cycle 1, but is able to continue on protocol following dose holding/dose reduction, they will still be considered a DLT.

Based on Gönen [31], we utilize a Bayesian interpretation for θ (the probability of DLT at a planned does; $\sim Beta(\alpha,\beta)$. The number of observed DLTs (X_s) in the safety lead-in cohort of N_s patients is assumed to follow a binomial distribution ($P(X_s|\theta) \propto \theta^s (1-\theta)^{N_s}$). Therefore, the posterior distribution of $P(\theta|X_s)$ is $Beta(\alpha+X_s, \beta+N_s-X_s)$. A uniform prior as

Beta(α=1, β =1) is used to reflect the uncertainty value for θ as suggested by Gönen [31].

Let N_s =15, the probability that θ exceeds various targets (i.e. 0.2, 0.3, 0.4) given the observed DLT patients' number ($P(\theta|X_s)$) can be calculated. They are listed in the following table:

DLT # in the 15 safety lead-in patients	P(θ>0.2)	P(θ>0.3)	P(θ>0.4)
0	0.028	0.003	0.000
1	0.141	0.026	0.003
2	0.352	0.099	0.018
3	0.598	0.246	0.065
4	0.798	0.450	0.167
5	0.918	0.660	0.329
6	0.973	0.825	0.527
7	0.993	0.926	0.716
8	0.999	0.974	0.858
9	1.000	0.993	0.942
10	1.000	0.998	0.981
11	1.000	1.000	0.995
12	1.000	1.000	0.999
>=13	1.000	1.000	1.000

Based on the table above, if we observe 0/15 patients with DLTs in the safety lead-in cohort, there is 0.003 chance that θ exceeds 0.3; whereas, if 5/15 patients with DLTs are observed, the chance that θ exceeds 0.3 increases to 0.660. Given these probabilities at the end of safety lead-in, we can make informed decisions regarding the appropriateness of the choice of the following trial (i.e. if >=5 DLTs observed in the safety lead-in cohort, the trial will be halted immediately and the PI will examine the toxicity profile and determine whether lower doses will be added).

14.2. Sample size calculation for the two-stage phase II trial

Prior targeted therapies for treatment of ovarian, primary peritoneal, and fallopian tube cancer have shown response rates of 0%-21% and PFS at 6 months of 6.5%-40.3% in patients with recurrent or advanced ovarian, primary peritoneal, or fallopian tube cancer and a history of 1-2 prior cytotoxic therapies.We hypothesize that treatment with enzalutamide will result in an increase in tumor response rate from 5% to 20% or an increase in 6-month PFS rate from 15% to 30% (Ho: π_{rr}<=0.05 and π_{pfs}<=0.15 vs. H1: π_{rr}>0.05 or π_{pfs}>0.15). To test the null hypotheses in a two-stage design, a method provided by Sill and Yothers [32] is used. In particular, in stage I, 28 eligible patients will be evaluated, if 3 or more patients have clinical response or 5 or more patients have no progression/death at 6 months, then the study will open to the second stage accrual. In

stage II, an additional 31 patients will be enrolled. At the end of stage II, if at least 7 of 59 (28+31=59) patients have clinical response or at least 13 of 59 patients survive progression free for 6 months, this will be considered as a positive trial.

Assuming the two primary endpoints are independent, the power in each scenario and the type 1 error are listed as in the following table:

		PFS rate at 6mo	
		π_{pfs}= 0.3	π_{pfs}= 0.15
Response	π_{rr}= 0.20	0.99	0.94
	π_{rr}= 0.05	0.90	0.10

Assuming the two primary endpoints are highly correlated (as the joint probability of π_{rr} and π_{pfs} is 0.90Xmin(π_{rr}, π_{pfs}) [32]), the power in each scenario and the type 1 error are as the following:

		PFS rate at 6mo	
		π_{pfs}= 0.3	π_{pfs}= 0.15
Response	π_{rr}= 0.20	0.97	0.92
	π_{rr}= 0.05	0.90	0.09

When the null hypotheses are true for both the response and the PFS, the chance of stopping the trial after stage I enrollment is 49% under independence and 55% under dependence.

The clinical response and the PFS from the starting of the treatment will be documented for each patient (including the patients in the safety lead-in). All the patients enrolled in this phase will be included in the main analysis of response and PFS. Patients who are lost to follow-up within 6 months are considered as failures for the PFS binary outcome of PFS within 6 months: yes/no. The response rate will be calculated. The patients accrued during the safety lead-in period will be included in the first stage of two-stage phase II portion. With the accrual rate of 3-6 patients per months, accrual of the 28 stage I patients should be complete within 9 months. After confirming promising results from stage I, the accrual of an additional 30 stage II patients should be complete within 10 months. The expected total trial duration is 30 months.

14.3. Other objectives

Safety and tolerability will be summarized using descriptive statistics. Adverse events will be assessed by NCI CTCAE version 4.0 criteria. The serious adverse events will be described separately.

The PFS duration will be summarized using the Kaplan-Meier method and the median PFS time will be estimated.

The treatment outcomes such as response rate and PFS will be associated with the AR expression (actual expression level, on a scale from 0-100%) by using Wilcoxon two sample test for relating to response and Cox PH model for relating to PFS.

The effect of enzalutamide (continuous) on levels of serum estradiol and testosterone and the effect on tumor AR expression by IHC will be described in graphical form and with descriptive statistics.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

This is a non-randomized study.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include data collection, abstraction and entry, data reporting, and problem resolution and prioritization.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

The estimated rate of accrual will be 5-6 patients per month. All patients will remain on treatment until POD, intolerable toxicity, self-discontinuation of study treatment, or removal from study for any other reason.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the

National Cancer Institute for Data and Safety Monitoring of Clinical Trials|| which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center‘s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)

- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting

professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

List appendices here. Appendices will be stored in a separate file and will be submitted in electronic and/or paper format. If electronic format, please submit on file per appendix.

Appendix A: Pill Diary
Appendix B: List of Medications that May Lower Seizure Threshold
Appendix C: Fact Card for patient reference