THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Phase II Study of the Levonorgestrel Intrauterine Device (Mirena) to Treat Complex Atypical Hyperplasia and Grade 1 Endometrioid Endometrial Carcinoma 2008-0094

Core Protocol Information

Short Title	Levonorgestrel IUD to Treat CAH and G1EEC
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Full Title:	A Phase II Study of the Levonorgestrel Intrauterine Device (Mirena) to Treat Complex Atypical Hyperplasia and Grade 1 Endometrioid Endometrial Carcinoma
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective

1.1.1 To determine the efficacy of the Levonorgestrel Intrauterine Device (IUD) to treat complex atypical hyperplasia (CAH) and grade 1 endometrioid endometrial carcinoma (G1 EEC).

1.1.2 To determine if response to therapy can be predicted based on the molecular profile of the tumor or by change in gene expression after therapy.

1.2 Secondary Objectives

1.2.1 To assess quality of life outcomes in patients treated with Levonorgestrel IUD.

1.2.2 To document the toxicity profile of the Levonorgestrel IUD in the treatment of complex atypical hyperplasia and grade 1 endometrioid endometrial cancer.

1.2.3 To evaluate the molecular profile of the hysterectomy specimen of patients treated with the Levonorgestrel IUD. Compare molecular profile in pretreatment tissue to hysterectomy tissue between responders and non-responders to Levonorgestrel IUD therapy.

1.2.4 To evaluate long-term survival, disease status, and fertility outcomes in patients with Levonorgestrel IUD.

2.0 Background

2.1 Endometrial Carcinoma and Complex Atypical Hyperplasia

Endometrial cancer is the most common gynecologic cancer in the United States. The American Cancer Society estimates that in 2007 there will be 39,080 new cases and 7,400 deaths from this disease[1]. The standard of care for early grade disease is complete surgical resection[2]. However, this may not be the preferred option in young women who have not completed childbearing. Furthermore, women with endometrial carcinoma may be suboptimal surgical candidates secondary to the presence of morbid obesity and multiple co-morbid conditions. This stems from the fact that these health conditions and endometrial cancer share many risk factors[3].

Complex atypical hyperplasia (CAH) is a precursor lesion to the most common histology of endometrial carcinoma, endometrioid type. In fact, in a study of 170 women with untreated endometrial hyperplasia, 29% of CAH progressed to endometrial carcinoma[4]. Trimble et al demonstrated that 42% of women with CAH on endometrial biopsy had a concurrent diagnosis of endometrial carcinoma on their subsequent hysterectomy specimen[5]. These data indicate that the two conditions are closely related, and often may be present together.

Furthermore, the initial diagnosis of CAH versus grade 1 endometrioid endometrial carcinoma (G1EEC) can be difficult to make. In the Trimble study, three gynecologic pathologists were unable to reach a consensus diagnosis in 16 of 289 endometrial biopsy specimens. Of those patients, 10 had carcinoma on their hysterectomy specimen[5]. An assessment of the reproducibility of CAH diagnosis in the setting of a Gynecologic Oncology Group trial revealed only 38% agreement with the initial diagnosis of CAH by a consensus panel. 30% of the biopsies with incorrect diagnoses were noted to be adenocarcinoma[6]. Given their close association and the difficulties in distinguishing between the two diagnoses, the inclusion of both entities in a treatment trial is reasonable.

2.2 Rationale

One of the most well-established risk factors for the development of CAH and endometrial

carcinoma is exposure to unopposed estrogen. In fact, a majority of the key conditions associated with endometrial cancer are directly or indirectly related to estrogen. Progesterone is known to counteract the effects of estrogen in the endometrium, thus, it has been used as a primary therapy for CAH and as an alternative primary therapy or adjuvant therapy for endometrial cancer[2].

Progesterone has been demonstrated to be an acceptable and efficacious option for treatment of complex atypical hyperplasia and grade 1 endometrioid endometrial carcinoma[3,7]. Despite the success of progesterone treatment, many women do not tolerate the side effects of systemic progesterone or are unable to maintain compliance with this therapy[8]. Montz et al evaluated the use of a progesterone releasing intrauterine device (Progestesert) to treat stage 1a, grade 1 endometrioid endometrial carcinoma. They demonstrated complete regression of G1EEC in 7 of 11 patients at 6 months and in 6 of 8 patients at 12 months[9]. Unfortunately, this therapy is no longer available for therapeutic use. The Levonorgestrel Intrauterine Device (LIUD) has been demonstrated to provide a consistent dose of progesterone to the uterine cavity with minimal systemic effects[10]. The toxicity of this treatment is low, with the most common complications consisting of irregular bleeding, expulsion, or uterine perforation during placement[11].

The studies of the LIUD for complex atypical endometrial hyperplasia are promising, but have been limited by low numbers. In a study of endometrial hyperplasia, there was regression of disease in 100% patients (n=26) treated with the LIUD compared to only 55% of patients treated with oral progesterone. It is important to note that only two of the patients in this study had CAH[12]. Wildemeersch et al noted 100% regression after Mirena placement in the eight patients with complex atypical hyperplasia in their study[13].

The use of the Mirena for the treatment of grade 1 endometrioid endometrial carcinoma has been less well studied, with only a few cases documented in the literature. Giannopoulos et al reported complete regression of a well-differentiated endometrial carcinoma after treatment with the LIUD[14]. Other case series, however, have had lower rates of success. Bahamontes et al treated two women with morbid obesity and G1EEC with the Mirena while awaiting gastroplasty for weight reduction. Both women had residual G1EEC in their hysterectomy specimens after 6 and 7 months, respectively[15,16]. In a case series of four women with G1EEC treated with LIUD, only one woman had complete regression at 6 months[16]. A larger study is necessary to clarify if the LIUD is effective in the treatment of grade 1 endometrioid endometrial carcinoma.

Given the success of oral progesterone for the treatment of both conditions, the LIUD is a rational option for patients with CAH and grade 1 endometrioid endometrial carcinoma. However, the existing literature is conflicting regarding the success of this treatment. Therefore, we propose a phase II trial to assess the efficacy of the LIUD for treatment of complex atypical hyperplasia or Grade 1 endometrioid carcinoma. Patients will receive this treatment for one year, as the median time to complete regression of G1 EEC during oral progesterone therapy is generally 12 weeks, with a range of 4 – 60 weeks[3].

2.3 Correlative Studies

In an earlier study, we discovered a cadre of genes which were highly induced in the endometrium of postmenopausal women after 3 months of treatment with estrogen therapy. These included PR, EIG121, IGF-I, RALDH2, sFRP1, and sFRP4[17]. Given that estrogen excess is a key factor in the development of hyperplasia and endometrioid type endometrial carcinoma, we subsequently studied the expression of these genes in a cohort of endometrial carcinoma patients. We found that G1EEC demonstrates high expression of these estrogen-induced genes[17]. Given the antagonistic effect of progesterone, these genes should be down-regulated after progesterone treatment.

Additionally, McCampbell et al demonstrated a step-wise increase in IGF-IR expression along the continuum from normal endometrium to G1EEC[18]. Our data confirmed that IGF-IR was highly

expressed in G1EEC, but had decreasing expression with increasing grade[17]. As this protein is known to be involved in an estrogen-regulated endometrial proliferation pathway, it is a rational target to include in our mRNA analysis. We plan to perform quantitative real time reverse transcriptase polymerase chain reaction for the aforementioned genes in the pre-treatment D&C specimen and 3-month post-treatment biopsy. These studies will provide pharmacodynamic evidence that the LIUD is having an effect on the endometrium. This time frame is based on results from our NCI-funded study of chemoprevention in patients with Lynch Syndrome without endometrial disease, which demonstrated a change in biomarker expression after three months treatment with progesterone-based therapy[19].

In 2007, we found that loss of PTEN and activation of mTOR were associated with poor response to progesterone in a murine hyperplasia model[20]. Given the need for markers which predict response to therapy in these patients, we will perform immunohistochemistry for PTEN and phosphorylated mTOR on paraffin-embedded tumor specimens.

3.0 Background Drug Information

Levonorgestrel Intrauterine Device (Mirena)

3.1 Description[11]
The Mirena releases a consistent dose of progesterone to the uterine cavity for five years. Its primary indication is contraception.

3.2 Mechanism of Action[11]
The Mirena releases 20ìg of levonorgestrel into the uterine cavity daily for five years. Levonorgestrel is bound primary in the serum to proteins and is metabolized into a large number of inactive metabolites. Metabolic clearance rates may differ among individuals by several–fold. The elimination half-life of the oral form is approximately 17 hours. Both levonorgestrel and its primary metabolites are excreted primarily in the urine. It causes local progestogenic effects in the uterine cavity. Morphological changes of the endometrium are observed, including stromal pseudodecidualization, glandular atrophy, leukocytic infiltration and a decrease in glandular and stromal mitosis. Mirena provides effective contraception in 99.3% of women over a five-year span.

3.3 Drug Supply[11]
Mirena is commercially available. There will be no charge to the patient or their insurance company for the Mirena IUD. It will be provided free of charge as part of the study.

3.4 Storage[11]
Mirena can be stored at 25°C, but can tolerate temperatures between 15° – 30°C for short time periods. It should remain in its sterile package until use.

3.5 Preparation and Administration[11]
The Mirena consists of a T-shaped polyethylene frame with a steroid reservoir around the vertical stem. The reservoir consists of a cylinder, made of a mixture of levonorgestrel and silicone and is covered by a silicone membrane. It contains a total of 52 mg of levonorgestrel. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the body.

3.6 Toxicity Data[11]
The most serious adverse events are ectopic pregnancy (1/1000), sepsis (4 cases of Group A Streptococcus in 1999), and pelvic inflammatory disease. Other complications reported include irregular bleeding, embedment in the uterus, perforation of the uterus and ovarian cysts. Minor adverse reactions seen in more than 5% of subjects include abdominal pain, leukorrhea, headache, vaginitis, back pain, breast pain, acne, depression, hypertension, upper respiratory

infection, nausea, nervousness, dysmenorrhea, weight increase, skin disorder, decreased libido, abnormal pap smear and sinusitis.

4.0 Patient Eligibility

4.1 Inclusion Criteria

4.1.1 All patients with a diagnosis of complex atypical hyperplasia or endometrial biopsy within three months of study enrollment OR patients with a diagnosis of grade 1 endometrioid endometrial carcinoma on endometrial biopsy within three months of study enrollment in the presence of one or more of the following:
- desire for future fertility
- morbid obesity (body mass index > 40)
- multiple co-morbidities (ASA Class 3 or 4)

4.1.2 No prior treatment for diagnoses 4.1.1
4.1.3 Women of any racial or ethnic group.
4.1.4 Ability to comply with endometrial biopsies every 3 months
4.1.5 Willing and able to sign informed consent.
4.1.6 Age greater than 18 years.

4.2 Exclusion Criteria

4.2.1 Diagnosis of grade 1 endometrioid endometrial carcinoma without the presence of one of the 3 criteria mentioned in 4.1.1.
4.2.2 Diagnosis of grade 2 endometrioid endometrial carcinoma or higher on endometrial biopsy or on dilation and curettage specimen.
4.2.3 Evidence of extrauterine spread of disease on imaging or during surgical evaluation.
4.2.4 Congenital or acquired uterine anomaly which distorts the uterine cavity.
4.2.5 Acute pelvic inflammatory disease.
4.2.6 Acute liver disease or previously diagnosed liver tumor (benign or malignant).
4.2.7 Conditions associated with increased susceptibility to infections with microorganisms. Such conditions include, but are not limited to, AIDS, leukemia and IV drug abuse.
4.2.8 Genital actinomycosis.
4.2.9 Current carcinoma of the breast.
4.2.10 Current pregnancy.
4.2.11 Breastfeeding mothers.

5.0 Treatment Plan

5.1 Study Design

This study will be a Bayesian phase II, single arm clinical trial. The study will enroll up to 50 evaluable patients. All women with the diagnosis of CAH on endometrial biopsy will be eligible. Women with G1 EEC on endometrial biopsy will be eligible if they desire fertility sparing options, are morbidly obese (BMI $\geq$40), or have co-morbid conditions which preclude a major surgical procedure (ASA Class 3 or 4).

5.2 Patient Accrual

All eligible patients being seen at The University of Texas M. D. Anderson Cancer Center Department of Gynecologic Oncology will be identified from a list generated by the clinic. Their primary physician will be contacted and asked permission to contact the patient for discussion of the trial. All Gynecologic Oncology physicians, registered nurses, advanced practice nurses and clinical fellows will be made aware of the trial through presentations, meetings, and fliers in the clinic. Benign gynecologists within the department will also be made aware of the trial through the same mechanisms.

In addition, the trial will be opened at the MD Anderson Cancer Center Regional Care Centers and the Harris Health System (Lyndon B. Johnson General Hospital). Finally, local Houston

benign gynecologists will be informed of the trial through presentations and fliers, and will be asked to refer patients they feel are eligible for participation.

5.3 Pretreatment Evaluation

After signing the informed consent, the patients will follow one of two treatment plans depending on their initial biopsy diagnosis. All patients will undergo a urine pregnancy test (women of child bearing potential) and cervical cultures in clinic to rule out pregnancy and active cervical infection. Patients with G1 EEC will undergo clinical staging procedures including chest radiography and MRI of the abdomen and pelvis. This will be a routine MRI of the abdomen and pelvis with standard pulse sequences including dynamic gadolinium enhanced imaging of the uterus.

Women who are unable to undergo MRI due to morbid obesity or other contraindication will have a CT scan of the abdomen and pelvis and transvaginal ultrasound. For those patients who are unable to undergo CT due to morbid obesity, transvaginal ultrasound will be performed. Scans will be reviewed by the diagnostic radiology collaborator on the study. Women will be excluded if there is evidence of extrauterine spread of disease.

Both cohorts of patients (CAH and G1 EEC) will then undergo an exam under anesthesia (EUA) and a dilation and curettage (D&C) in the operating room to sample the entire endometrium. This specimen will be read by a certified gynecologic pathologist at our institution and report dictated in the electronic medical record. At the time of D&C, the LIUD will be placed. Women who have previously undergone D&C for this diagnosis will not be required to undergo a second D&C. The pathology specimen will be obtained for review and confirmation of diagnosis and for the correlative studies to be performed. The LIUD will then be placed in the clinic setting.

If patients with an initial diagnosis of CAH are upgraded to G1 EEC, they will be assessed for eligibility through inclusion criteria 1. If the patient does not meet inclusion criteria, they will be removed from the study. Otherwise, they will undergo chest radiography, and MRI of the abdomen and pelvis and/or CT of the abdomen and pelvis and/or transvaginal ultrasound as detailed aove in the post-operative period. Women will remain on study if they have confirmed CAH and/or G1 EEC on the D&C specimen and have no evidence of extrauterine spread of disease. If a woman is excluded from the trial after LIUD is placed, the LIUD will be subsequently removed. Removal of the LIUD can be performed in the operating room if the patient proceeds with surgical treatment or in the clinic.

5.4 Evaluation During Study

All subjects will be evaluated at one month (+/- 1 week) after LIUD placement to confirm the placement of the LIUD. This visit may be performed at MD Anderson or at the subject's local physician office, based on patient preference. Placement will be confirmed by speculum exam and, if necessary, using pelvic ultrasound.

Endometrial biopsy may be performed while the LIUD is left in situ. The endometrial biopsy will be performed with the Pipelle endometrial suction instrument (Cooper Surgical, Trumbull, CT). Each patient will have a follow-up endometrial biopsy every three months for one year (+/- 2 weeks). Endometrial evaluation every three months is the standard of care for patients with CAH or G1EEC undergoing conservative therapy. The pathology of the endometrial biopsies will be read by a certified gynecologic oncologist and report dictated in the electronic medical record.

The molecular profile of the endometrial lesion in the pre-treatment D&C specimen and 3-month post treatment biopsy will be determined. Using formalin-fixed, paraffin-embedded tissue, the mRNA expression profile will be determined by real time reverse transcriptase polymerase chain reaction for a panel of genes including PR, EIG121, IGF-I, IGF-IR, RALDH2, sFRP1, and sFRP4. The level of mRNA expression will be normalized by comparison to the expression of â-actin and 18S, two cellular housekeeping genes. See Appendix D for RT-PCR protocol. Protein expression

of PTEN and phosphorylated mTOR will be determined through the performance of immunohistochemistry on the formalin-fixed, paraffin-embedded endometrial biopsy specimens. See Appendix E for the immunohistochemistry protocol.

An evaluation of any complications related to the LIUD will be completed at each follow-up visit by study personnel. This assessment can be found in Appendix F. It includes concerns which are specific to the LIUD as well as typical side effects of systemic progesterone therapy. In addition, the patient will be given a diary to fill out at home during the first 3 months after LIUD placement. This diary is provided by Bayer and monitors vaginal bleeding after LIUD placement. See Appendix I for this diary.

Finally, quality of life assessment will be performed at baseline and at each 3 month follow-up visit using the SF-36 instrument (Appendix G). This 36-question validated instrument is a generic measure which incorporates an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. These results will be compared to available standardized results from this instrument. This is intended to provide pilot data for future trials including the LIUD.

5.5 Criterion for Response

Response is defined as follows:

Complete response is defined as no endometrial abnormality or the presence of endometrial hyperplasia without cytologic atypia at the one year time point.

Partial response is defined as the presence of complex endometrial hyperplasia with cytologic atypia in patients with an initial diagnosis of grade1 endometrial cancer, at the one year time point.

Stable disease is defined as no change in diagnosis at the one year time point.

Progressive disease is the presence of grade 2 cancer or above in patients with an initial diagnosis of grade 1 cancer OR presence of grade 1 cancer or above in patients with an initial diagnosis of complex atypical hyperplasia at any time point.

Patients with stable disease or progressive disease will be categorized as non-responders for the purposes of molecular analysis.

5.6 Criteria for Removal From Study

At the one year time point the patient will complete the study. If progression of disease is noted at any time, the patient will be taken off study and at the physician's discretion, the LIUD may be removed and the patient will be treated with either definitive surgical therapy or an alternative progesterone agent. In the case of G1 EEC, progression will be defined as the presence of grade 2 endometrioid cancer or worse on the endometrial biopsy. In the case of CAH, progression will be defined as G1 EEC or worse on the endometrial biopsy. The patient will also be removed from the study and offered alternative therapies if unacceptable toxicity or complications occur due to the LIUD.

5.7 Study Completion

The patients that complete of one year of therapy will be offered continuation of the LIUD, hysterectomy, or alternative progesterone therapy. If they choose to continue LIUD treatment, they will be referred to their primary gynecologic oncologist for continued management and follow-up. The LIUD may remain in situ for five years. If they choose to have the LIUD removed they will be referred back to their primary gynecologic oncologist to discuss further options and management.

A molecular profile will be performed on the uterine specimen of any protocol patients that

undergo hysterectomy for progressive disease or at the completion of therapy. This profile is including, but not limited to, determination of expression of estrogen-induced genes and expression of PTEN and phosphorylated S6 protein by IHC. Current and future patients from MD Anderson Cancer Center and Harris Health System (Lyndon B. Johnson General Hospital) will be consented for this optional tissue collection. For MD Anderson patients who are no longer on study, we will ask for a waiver of consent to collect retrospective tissue as it may be difficult to locate these patients or they may be deceased and this tissue collection will pose minimal risk to the patients. We will use previously signed consent from the IRB approved Gyn Onc Tumor Bank protocol (LAB02-188) or the MD Anderson front door consent protocol (Lab03-0320)

5.8 Long-term Follow-up

All patients will be followed for 5 years from their last study-specific intervention, unless consent is withdrawn or the patient is lost to follow-up. No clinic visits or other patient contact is required for follow-up. Patient survival, disease status, and fertility outcomes will be followed annually through review of their medical record.

5.9 Patient Flow Diagram

Please see Appendix H for Patient Flow Diagram.

6.0 Correlative Studies

6.1 Gene Expression

6.1.1 Collection of Sample

6.1.1.1 Dilation and Curettage

This sample will be collected in the operating room. Upon collection, the specimen will be formalin-fixed and taken to the laboratory at room temperature.

6.1.1.2 Three-Month Endometrial Biopsy

This sample will be collected in the clinic room using the Pipelle collection device. Adequate tissue amount will be determined by the clinician and research coordinator collecting the specimen. Upon collection, the specimen will be formalin-fixed and taken to the laboratory at room temperature.

6.1.2 Handling of Sample

6.1.2.1 Dilation and Curettage and Three-Month Endometrial Biopsy

A hematoxylin and eosin slide will be prepared for the gynecologic pathologist to read and obtain diagnosis. The remainder of the tissue will be divided for PCR and IHC. RNA extraction will be performed on the tissue and the resultant RNA will be stored in the -80°C refrigerator until analysis.

6.2 Immunohistochemistry

6.2.1 Collection of the Sample

6.2.1.1 Dilation and Curettage

This sample will be collected in the operating room. Upon collection, the specimen will be formalin-fixed, processed by the pathologist, and taken to the laboratory at room temperature.

6.2.1.2 Three-Month Endometrial Biopsy

These samples will be collected in the clinic room. Adequate tissue amount will be determined by the clinician and research coordinator collecting the specimen. Upon collection, the specimen will be formalin-fixed, processed by the pathologist, and taken to the laboratory at room temperature.

6.2.2 Handling of Sample

6.1.2.1 Dilation and Curettage and Three-Month Endometrial Biopsy
A hematoxylin and eosin slide will be prepared for the gynecologic pathologist to read and obtain diagnosis. The remainder of the tissue will be divided for PCR and IHC. Four slides will be cut from the formalin-fixed, paraffin-embedded tissue for performance of immunohistochemistry.

6.2.3 Scoring of IHC Results

6.2.3.1 PTEN
Loss of PTEN expression will be defined as no staining in greater than 10% of the endometrial glands in the specimen[20].

6.2.3.2 Phosphorylated mTOR
Positive expression of phosphorylated mTOR will be defined as moderate (2+) to strong (3+) staining in greater than 20% of the endometrial glands in the specimen[20].

7.0 Statistical Considerations

7.1 Sample Size Calculation
A Bayesian Phase II design was employed for sample size calculation. We will enroll and evaluate a minimum of 20 evaluable (those who complete 12 months of therapy) patients and a maximum of 50 evaluable patients in this study.

7.2 Early Stopping for Futility

We will stop the trial early if Pr (success rate < 65% | data) < 0.05.

This means that, given the outcomes of patients who have already completed the trial, if we determine that there is less than a 5% chance that the success rate of LIUD is at least 65%, we will stop the trial. We assume that the prior distribution for the success rate is Beta (1.3, 0.7), which has a mean of 65% and a standard deviation of 27.5%.

Therefore, we will stop the trial if:

[# of patients with complete remission / # of patients evaluated]
9/20, 10/22, 11/24, 12/25, 13/27, 14/29, 15/31, 16/32, 17/34, 18/36,19/38, 20/39, 21/41, 22/43, 23/44, 24/46, 25/48, 26/49.

For example, if only 9 patients had complete remission by the time 20 patients completed the study, we will terminate the study due to futility, as there is very little evidence (< 5% chance) that the success rate is at least 65% if 9 or fewer of 20 patients had a complete remission.

The operating characteristics of this monitoring rule are shown in Table 1.

Table 1. Operating Characteristics of the Futility Monitoring Rule

True Treatment Success	Probability of Stopping Early	Sample Size		
		P25	P50	P75
0.50	0.793	20	25	44
0.55	0.568	22	43	50
0.60	0.317	38	50	50

0.65	0.133	50	50	50
0.70	0.037	0	50	50
0.75	0.007	50	50	50
0.80	0.001	50	50	50

If the true treatment success rate is really 65% we have a 13.3% chance of stopping the trial early due to futility. If the true treatment success rate is really 50% we have a 79.3% chance of stopping the trial early due to futility. In this case 25% of the time we would have treated 20 patients or fewer at the time of stopping the trial, 50% of the time we would have treated 25 patients or fewer at the time of stopping the trial, and 75% of the time we would have treated 44 patients or fewer at the time of stopping the trial.

7.3 Endpoints
The primary outcome will be response to therapy, which is defined as complete response or partial response (detailed in section 5.5), assessed at the one year endometrial biopsy. Secondary outcomes will include toxicity and complication information. The molecular profile will be utilized to determine if response to therapy can be predicted. Additionally, toxicity assessment and quality of life assessment with the SF-36 survey will be performed at baseline and at each 3-month follow up visit as described in Section 5.4.

7.4 Analysis of primary outcome
Once we have completed the study, we will estimate the treatment success rate with a 90% credible interval. For example, if 27 of 50 patients (54%) have complete remission, the 90% credible interval for the treatment success rate will be 43.1% to 65.6%. If 35 of 50 patients (70%) have complete remission, the 90% credible interval for the treatment success rate will be 59.0% to 79.7%.

If the upper bound of the 90% credible interval is less than our goal of 65% success rate, we will not pursue further study of this intervention.

7.5 Analysis of secondary outcomes
A secondary aim of this study is to determine whether treatment success is related to a patient's genetic profile. To this end, we will measure PR, EIG121, IGF-I, RALDH2, sFRP1, sFRP4, and IGF-IR at baseline and again at the 3-month biopsy. Change from baseline (*ä*) for each biomarker will be calculated and the hypothesis that

H0: *ä* = 0 vs. H1: *ä* · 0

will be tested with a paired t-test. Because genetic profile information is highly skewed, natural log transformations will be made to the data prior to calculating change from baseline and completing the t-test. Previous data indicate that the standard deviation of the log-transformed data will be approximately 1. Table **2** shows the power of our test when we use a statistical significance level of 5%, both when the standard deviation is 1 and again if the standard deviation should be 1.25, slightly larger than we estimated. Power was assessed at sample sizes n = 20, 25, 30, 35, 40, 45 and 50 because our actual sample size might range anywhere between 20 and 50 patients.

Table 2. Power to Determine Changes in Genetic Profile (*á* = 5%, two-sided test, hypothesized difference of 0.5)

Sample Size	Power	
	When SD = 1	When SD = 1.25
20	56.45%	39.70%
25	66.97%	48.40%

30	75.40%	56.28%
35	81.95%	63.28%
40	86.94%	69.40%
45	90.66%	74.68%
50	93.39%	79.18%

Although we might stop the trial early, our median sample size is most likely 50, and therefore we should have at least 79% power to detect a difference of 0.5 in our genetic profile data.

Change in immunohistochemical expression will be analyzed for association with response using a chi-square analysis.

Summary statistics will be calculated for quality of life scores, both at baseline and every three months afterwards until the patient completes the study. This analysis will be descriptive.

Summary statistics will also be completed on LIUD toxicity. The LIUD toxicity profile is known to be low, and it tends to be well-tolerated, therefore we do not anticipate a need to stop the trial early due to toxicities. However, incidence of toxicities will be calculated.

We will calculate period prevalence and incidence of recurrence along with 95% confidence intervals. Period prevalence is calculated as the number of patients who recur divided by number of patients at risk for recurrence. Incidence is calculated as the number of patients who recur divided by person-time follow-up. Recurrence is defined as return to original disease state or worse after being disease-free. Finally, the proportion of patients who return to a worsening disease state after an initial response will be calculated. Specifically, it will calculate the proportion of patients who have progressive disease if their best response was stable disease, partial response, or complete response.

Summary statistics will be calculated for disease status and fertility outcomes. This analysis will be descriptive.

We will calculate period prevalence and incidence of recurrence along with 95% confidence intervals. Period prevalence is calculated as the number of patients who recur divided by number of patients at risk for recurrence. Incidence is calculated as the number of patients who recur divided by person-time follow-up. Recurrence is defined as return to original disease state or worse after being disease-free. Finally, the proportion of patients who return to a worsening disease state after an initial response will be calculated. Specifically, it will calculate the proportion of patients who have progressive disease if their best response was stable disease, partial response, or complete response.

Summary statistics will be calculated for disease status and fertility outcomes. This analysis will be descriptive.

8.0 Data and Protocol Management

This study is planned as a multi-site study. All patients will be centrally registered into the Clinical Oncology Research System (CORe) at M. D. Anderson Cancer Center. Information will include a completed eligibility check list, patient name, date of birth, consent date, and race. Once accrual is complete, study data will be combined for analysis.

Protocol Compliance: The study research nurse will be present at each visit to ensure compliance with protocol guidelines. Decisions for removal from study based on response will be made by the Study Chairman and the Study Pathologist (RRB).

Data Entry: Data must be entered into the Gyn Oncology Departmental database for this protocol.

Accuracy of Data Collection: The Study Chairman will be the final arbiter of response or toxicity should a difference of opinion exist.

9.0 Adverse Event Reporting

9.1 Reporting Adverse Events

All **Internal** and **External** AEs that include all of the following will be promptly reported to IRB via the Office of Protocol Research (OPR):

- Serious
- Unexpected
- Related (definitely, probably, or possibly related) to participation in the research.

Timeline for prompt reporting of Internal AEs:

1. **Within 1 working day (24 hours) from the time the research team becomes aware of the event =** All deaths that occur during treatment and within 30 days after completion of treatment.

2. **Within 5 working days from the time the research team becomes aware of the event =** All serious, unexpected and related AEs other than those deaths described above in number 1.

Internal SAEs will be reported from the time protocol specific consent is signed, and screening or treatment has begun, during the course of treatment and within 30 days after the last day of active treatment.

Beyond 30 days of treatment, completion of only those SAEs that, in the judgment of the investigator, are related to research will be reported.

Reporting Timeline for prompt reporting of External AEs:

1. **Within 5 working days from the time the research team becomes aware of the event =** All related deaths that occur during treatment and within 30 days after completion of treatment.

2. **Within 5 working days from the time the research team becomes aware of the event =** All serious, unexpected and related AEs other than those deaths described above in number 1.

External SAEs will be reported to the IRB beginning on the date of the UTMDACC IRB approval letter of the associated protocol.

SAEs Requiring Documentation on AE Log:

All SAEs that do not fall under the prompt reporting requirements will be reported during continuing review using the **Internal** or **External** SAE Log or database printout.

Note: If a trend or recurring adverse events are seen, the PI will report these events using the **Internal** or **External** SAE report Form for prompt reporting.

These reporting guidelines do not affect the reporting requirements to the FDA, the sponsor or monitoring agency.

Reporting for trials involving minimal risk
For protocols designated as minimal risk, AEs considered serious, unexpected and definitely, probably or possibly related to the study will be reported promptly as described above. [AEs considered to be unrelated to the study and non-serious AEs will be reported during continuing review (annual report)].

Reporting of SAEs for Terminated Protocols
Only those serious AEs that were unexpected and may impact the health, welfare or safety of subjects will be reported. For example, reports of secondary malignancies or problems with implanted devices.

DEFINITIONS
Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

For minimal risk studies such as behavioral science, laboratory, and epidemiologic protocols, as well as chart reviews, reasonable judgment must be used to determine what constitutes an AE.

Expected AE - Any AE with specificity or severity that is consistent with the current Investigator Brochure (IB) or consistent with the risk information described in the Informed Consent Document (ICD) or general investigational plan. All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment.

Unexpected (Unanticipated) AE - Any AE, with specificity or severity that is not consistent with the current IB or not consistent with the risk information described in the ICD or general investigational plan.

Serious Adverse Event (SAE) – Any AE associated with the subject's participation in research that:
- results in death;
- is life-threatening, (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Internal AE - An AE occurring in a subject who is enrolled in a protocol or study that is under the oversight of a UTMDACC IRB.

External AE – An AE occurring in a subject who is not enrolled in a UTMDACC protocol or is on a protocol at a site that is under the oversight of another IRB. Generally, the PI has received notification of this AE from the protocol sponsor. Example: Medwatch report, CIOMS report, Safety reports.

Related:
Events directly or indirectly attributed to study drug, device or procedures and/or study participation. Events occurring with sufficient frequency to suggest that they are not random.

Unrelated:
Events that would occur regardless of study participation, including events that are clearly random occurrences. If the frequency of the event suggests a possible connection to the study

intervention, then it should be considered related.

AE Attribution - The determination of whether an AE is related to the research (medical treatment or intervention):

Definite – It is clearly related
Probable - It is likely related
Possible - It may be related
Unlikely - It is doubtfully related
Unrelated - It is clearly NOT related

AE Severity - Refers to the intensity (grading) of a specific AE. All clinical trials conducted at UTMDACC must use the "CTCAE v3.0 grading scale" for AE documentation and reporting (Publish date June 10, 2003). For the purpose of this policy, toxicity is synonymous with AE.

Minimal Risk - Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of a routine physical examination, physiological examination or laboratory testing.

Designation of minimal risk will be determined by the IRB at the time of initial approval and reviewed at least annually during continuing review.

Multicenter Studies
Since UTMDACC PIs participating in multicenter trials are unable to prepare a meaningful summary of SAEs, at the time of continuing review they should submit the current report from the monitoring entity (e.g. research sponsor, coordinating statistical centre, or DSMB/DMC). The report should include the following:

- a statement as to what information was reviewed by the monitoring entity (e.g. study-wide AEs, interim findings, recent literature relevant to the research);
- date of the review;
- monitoring entity's assessment of the information. Information that is considered inadequate by the PI should be returned to the monitoring agency/sponsor for completion

9.2 Eliciting Adverse Event Information
Adverse events will be elicited at each clinic visit during participation in the study. Patients will be given a worksheet to record the occurrence of adverse events throughout the study. All adverse events which are directly observed and all adverse events which are spontaneously reported by the patient are to be documented by the investigator.

9.3 Grading/Rating Scale
All adverse events reported during the study will be evaluated and graded on a scale of 1-4.

Grade	Rating	Description
1	Mild	Adverse event is transient and easily tolerated by the patient; asymptomatic
2	Moderate	Adverse event causes the patient discomfort and interrupts the patient's usual activities; symptomatic but does not interfere with function
3	Severe	Adverse event causes considerable interference with the patient's usual activities
4	Life-Threatening	Adverse event is incapacitating or life-threatening

10.0 Data Confidentiality Plan

On enrollment, patients will be assigned a study number. All study documents will be de-identified of any patient information such as name, social security number, date of birth, or medical record number. Data collection files will be stored in a locked file cabinet. The document which links the identifiable patient information to a study number will be stored in a password-protected computer file. Once the data have been analyzed, all identifiers will be destroyed.

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