LEVER Trial: Levonorgestrel Intrauterine Device Alone or in Combination with an mTORC1 Inhibitor to Overcome Progesterone Resistance in Atypical Hyperplasia or Stage Ia Grade 1 Endometrioid Endometrial Cancer

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BACKGROUND

- Endometrial cancer is the most common gynecologic cancer in the United States with over 66,000 women diagnosed in 2020.
- The standard of care for early stage endometrial cancer is complete surgical resection.
- The average age for women diagnosed with endometrial cancer is 60 years, however, 25% of patients are premenopausal and many are still of childbearing age.
- Surgical resection may not the ideal course of action for young women who want children in the future or women who are unable to have the surgery performed due to medical co-morbidities.
- The levonorgestrel intrauterine device (LIUD) releases a consistent dose of progesterone into the uterine cavity for five years.
- LIUD has been used in lieu of a surgical resection for atypical hyperplasia (AH) and grade 1 endometrioid endometrial carcinoma (EEC) with response rates for 85% and 65%, respectively, but resistance to progesterone can be observed.

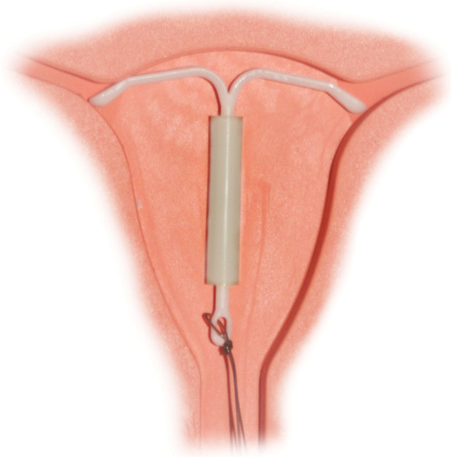


Figure 1. The levonorgestrel intrauterine device (LIUD)

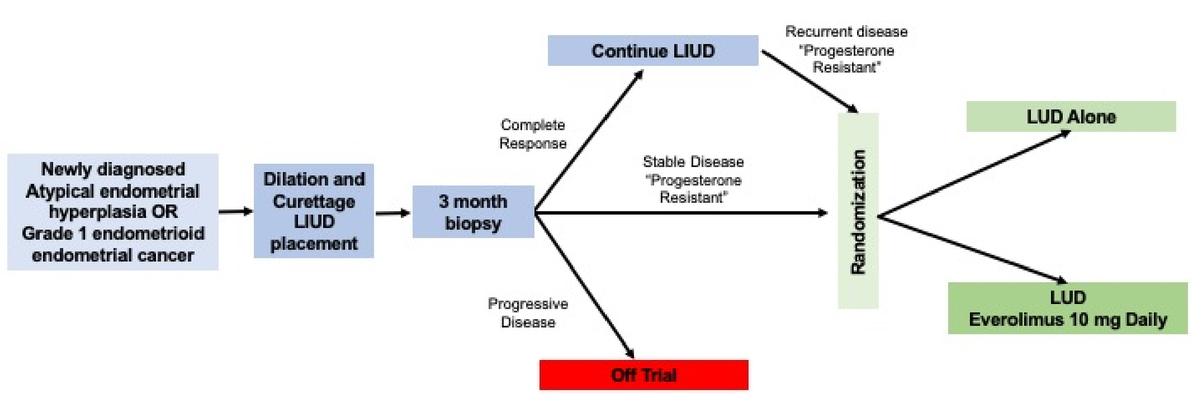
AIM

- This trial will study the levonorgestrel intrauterine device (LIUD) alone or in combination with an mTORC1 inhibitor (everolimus) to overcome progesterone resistance in AH or stage Ia grade 1 EEC.
- In addition, we will assess clinical, pathologic, and molecular factors associated with progesterone resistance.

METHODS

- This multicenter study is a two-stage, randomized phase II trial of the LIUD alone or in combination with everolimus for the treatment of patients with AH or stage Ia, grade 1 EEC.
  - Patients will have adequate organ and bone marrow function.
  - Well controlled diabetes is permitted on study.
- In the first stage , patients without prior treatment with have LIUD placed at the time of confirmatory dilation and curettage.
  - Biopsy obtained after 3 months of treatment.
  - Those patients that have residual disease are deemed progesterone resistant and proceed to the second stage.
  - Patients with LIUD in place for at least 3 months prior to study that have residual disease are deemed progesterone resistant will progress immediately to second stage.
- In stage 2, if progesterone resistance is identified, patients are randomized to either the LIUD alone or in combination with everolimus.

STUDY SCHEMA



ENROLLMENT

- Approximately 270 women with AH or grade 1 EEC will participate in the first stage of the study.
- We will randomize 80 patients in the second stage to achieve adequate power to detect difference in response.
- For translational objectives, tissue is obtained at baseline, 3 months, and 6 months.
- Molecular factors, including baseline and change in gene/protein expression in relevant pathways such as PI3K/AKT, estrogen-regulation, and Wnt signaling, will be associated with response and resistance to therapy.

Table 1: Current patient enrollment on LEVER trial

Site	Phase 1					Phase 2		
	Consented	Screen Fails	Evaluable Toxicity	Evaluable Response	CR	LIUD	Combo	TOTAL
MDACC	43	17	27	26	17	4	4	8
HALs	18	9	9	9	8	1	1	2
LBJ	14	3	10	10	8	1	3	4
Ohio Health	6	3	3	3	1	2	0	2
Cooper	2	0	0	0	0	0	0	0
UVA	9	4	2	2	2	1	1	2
Queen's	1	1	0	0	0	0	0	0
Oklahoma	1	1	0	0	0	0	0	0
Banner	1	0	0	0	0	0	0	0
Covenant	0	0	0	0	0	0	0	0
Northwell	0	0	0	0	0	0	0	0
TOTAL	95	38	51	50	36	9	9	18

OBJECTIVES

Primary:

- Estimate the efficacy of the LIUD alone to treat complex atypical hyperplasia or stage Ia grade 1 endometrioid endometrial carcinoma with response rate.
- Estimate the efficacy of the LIUD in combination with everolimus to treat LIUD-refractory complex atypical hyperplasia or stage Ia grade 1 endometrioid endometrial carcinoma with response rate.

Secondary:

- Document the toxicity profile of the LIUD alone or in combination with everolimus using the NIH- NCI Common Terminology Criteria for Adverse Events v4.0.
- Estimate overall survival (OS) and event-free survival (EFS) of patients with complex atypical hyperplasia or stage Ia grade 1 endometrioid endometrial cancer treated with the LIUD alone or in combination with everolimus.
- Estimate the response duration associated with the LIUD alone or in combination with everolimus in patients with complex atypical hyperplasia or stage Ia grade 1 endometrioid endometrial cancer.

Exploratory:

- Determine if response to therapy can be predicted based on the molecular profile of the tumor, including estrogen-induced genes and relevant pathway members, or by change in gene expression after therapy

RESULTS

- There have been 57 patients have been treated with the LIUD during the first stage of this ongoing study.
- 18 patients continued into stage 2 of the study with 9 being treated with LIUD alone and 9 with the combination of LIUD and everolimus.
- To date, tissue has been collected from 16 patients at all three time points.

CONCLUSION

- Tissue collection is feasible in a multicenter study.
- Analysis of the data collected on study is ongoing.