Gynecologic Oncology 211 (2026) 171–177

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Surgical window of opportunity clinical trial of abemaciclib and letrozole for endometrioid adenocarcinoma of the endometrium

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HIGHLIGHTS

- Abemaciclib and letrozole was tolerable for endometrioid endometrial cancer.
- Abemaciclib and letrozole induced significant reduction in cellular proliferation.
- Surgical window of opportunity studies permit evaluation of biological effects.

ARTICLE INFO

Article history:
Received 19 April 2026
Received in revised form 2 July 2026
Accepted 3 July 2026
Available online 14 July 2026

Keywords:
Surgical window of opportunity
Abemaciclib
Letrozole
Cellular proliferation
Ki-67

ABSTRACT

Background. Abemaciclib inhibits cyclin dependent kinases (CDK) 4 and 6 and, in synergy with anti-estrogens, is an FDA approved treatment of ER+ breast cancer. We hypothesized that letrozole and abemaciclib will inhibit cellular proliferation in patients with endometrial cancer.

Methods. This is a single-arm prospective multicenter surgical window of opportunity clinical trial for patients with endometrial cancer planned to undergo definitive management with hysterectomy. Patients received 14 days of abemaciclib 150 mg twice daily and letrozole 2.5 mg once daily. The primary endpoint was change in Ki-67 (%) from pretreatment biopsy to posttreatment hysterectomy specimen. Secondary endpoints included biological tumor characteristics (MMR, PTEN, PI3K, cyclin D1, pRB) associated with Ki-67 changes.

Results. Twenty seven women were enrolled, 2 patients withdrew consent leaving 25 evaluable patients. The median age was 62 (IQR: 54–66) and 19 patients (76%) were menopausal. Most patients were White (68%), 24% identified as Black; 20% were of Hispanic ethnicity. All cancers were endometrioid with the majority FIGO grade 1 (76%) and 24% grade 2. Seven (28%) patients had mismatch repair deficient tumors. Mean baseline Ki-67 was 34% (SD 22%). After 2 weeks of treatment, mean Ki-67 reduction was 19% (SD 23%, $p < 0.001$) meeting the prespecified endpoint. We found no significant difference in the magnitude of Ki-67 reduction based upon pRb, PTEN, cyclin D1, p16, or MMR proteins. There were no serious adverse events recorded.

Conclusions. Abemaciclib and letrozole induced a reduction in cellular proliferation in endometrioid endometrial cancer over a short two-week time period prior to surgery.

1. Background

Despite recent advances, recurrent endometrial cancer is an incurable malignancy with poor prognosis. Limited options exist for women with recurrent endometrial cancer after platinum-based systemic therapy. Immunotherapy in combination with chemotherapy or with lenvantinib has been approved for treatment of advanced and

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https://doi.org/10.1016/j.ygyno.2026.07.001
0090-8258/

recurrent disease [1,2]. Trials have shown that selected biologic targeted agents have modest to moderate activity in this setting (particularly bevacizumab and mTOR/PI3K inhibitors) [3–6]. Novel antibody drug conjugates are being tested in this setting. There remains a need to develop new targeted strategies for patients with metastatic and/or recurrent endometrial cancer.

Unopposed estrogen signaling has been implicated as a driver both in the etiology and in the progression of endometrioid endometrial cancer and hormonal therapy plays a role in the management of estrogen receptor (ER) or progesterone receptor (PR) expressing endometrial tumors [7]. Progestins induce cellular differentiation and remain the most active hormonal intervention for endometrial cancer. Several studies have tested medroxy-progesterone in patients with recurrent endometrial cancer. The observed response rates ranged from 17% to 33%, the median progression free survival (PFS) was 3–4 months and overall survival (OS) was 11–13 months [8–11]. Strong correlations between low histological grade and hormone receptor expression (both ER and PR) and response were recorded [9].

Suppression of estrogen signaling represents another therapeutic angle. Several interventions have been tested (selective estrogen receptor modulators, gonadotropin releasing hormone analogs, aromatase inhibitors) and have shown only modest activity as single agents [7]. Aromatase inhibitors (AIs) block the conversion of androgens to estrogen in post-menopausal women. The malignant endometrium expresses aromatase which contributes to in situ estrogen synthesis [12,13], supporting the testing of AIs in this setting. Response rates to anastrozole in unselected patients with recurrent EC were 9% (2 PRs in 23 patients), however more than half of patients in this cohort had grade 3 EC and the ER/PR status was not reported [14]. Exemestane induced a response rate of 10% in patients with ER+ tumors, with 35% remaining free of disease free progression at 6 months [15]. Likewise, letrozole induced a 9% response rate and 30% stable disease for a median duration of 6.7 months in a trial of the NCI Canada [16]. Neo-adjuvant 2 week treatment with anastrozole partially suppressed endometrial cancer proliferation as measured by Ki-67 [17]. As AIs are very well tolerated, there is interest in optimizing their use, by designing rational combinations to exploit synergy with other pathway inhibitors and by identifying select populations likely to benefit. Indeed, the combination of letrozole and mTOR inhibitor (everolimus) induced a 32% response rate in an unselected group of endometrial cancer patients [18] and the clinical benefit rate was 65% among patients with ER+ endometrioid tumors. A more recent randomized phase II study found a response rate of 22%, supporting that combinations targeting key vulnerabilities of endometrial cancer cells, such as estrogen pathways, have therapeutic benefit [19].

It is known that cyclin D1 is a direct transcriptional target of ER signaling [20] and that the activity of cyclin dependent kinases (CDKs) is regulated by estrogen-engaged mechanisms [21–23]. Synergy between anti-estrogens and CDK inhibitors has been observed in ER+ breast cancer cells [24] and the combination of letrozole and palbociclib significantly increased the PFS in patients with metastatic ER+ breast cancer (Paloma 1 trial, $p < 0.000001$) [25]. Cell lines resistant to anti-estrogen therapy have been shown to lack RB induced transcriptional repression [26] and to be susceptible to therapeutic interventions targeting CDK4/6. Furthermore, clinical activity of anti-estrogens (fulvestrant) in combination with CDK4/6 inhibitors was also observed in metastatic ER+ breast cancer patients resistant to endocrine therapy (Paloma 3) [27]. In endometrial cancer the enzymatic activity of CDK4 and 6 has been shown to correlate with proliferative indices (Ki-67) and with PFS, independently of other clinical prognostic factors [28].

Based on the knowledge that ER signaling drives tumorigenesis for endometrioid endometrial cancer and that estrogen is a critical regulator of the cell cycle regulatory machinery in cancer cells, it is reasonable to hypothesize that the combination of aromatase and cyclin dependent kinase inhibitors are active in endometrial cancer. The combination of CDK 4–6 inhibitors have been studied in small phase II studies of estrogen receptor positive metastatic and recurrent endometrial cancer. Response rates of 30–44% were observed [29,30]. The activity of the regimen in early-stage endometrial cancer has not been studied. A surgical window of opportunity design allowed for enrollment of these patients and the ability to evaluate the effects of this combination in this population during the short preoperative period. In endometrial cancer, where molecular heterogeneity is increasingly recognized, window of opportunity studies can help stratify patients by response and inform further development of therapies.

We hypothesized that the combination of letrozole and abemaciclib will decrease cellular proliferation, as measured by Ki-67, in patients with endometrioid endometrial cancer when taken for 14 days prior to definitive hysterectomy. The primary objective was to determine the magnitude of change in Ki-67 expression from the pretreatment specimen (e.g. biopsy or D&C) to the post-treatment hysterectomy specimen following 2 weeks treatment with letrozole and abemaciclib.

2. Methods

2.1. Study design

This is a single-arm prospective multicenter surgical window of opportunity clinical trial for patients with endometrial cancer planned to undergo definitive surgical management with hysterectomy. The primary endpoint was the change in Ki-67 (%) from pretreatment biopsy to posttreatment hysterectomy specimen. Secondary endpoints included biological tumor characteristics (MMR, PTEN, PI3K, cyclin D1, pRB) associated with Ki-67 changes. Patients received treatment with 14 days of abemaciclib 150 mg twice daily and letrozole 2.5 mg once daily with the last dose taken the day prior to surgery. This investigator-initiated study was approved by the Institutional Review Board at Northwestern University and was registered at clinicaltrials.gov (NCT04049227). Funding and abemaciclib were provided by Eli Lilly and Company. All patients provided written informed consent prior to study enrollment.

2.2. Eligibility

Patients with endometrioid endometrial cancer who were planned for definitive surgical management with hysterectomy were eligible. Additional inclusion criteria were any grade endometrioid endometrial cancer; treatment naïve without previous endometrial cancer directed therapies; ECOG performance status of 2 or less; and adequate organ function including ANC ≥1.5×10^9/L, platelets ≥100×10^9/L, hemoglobin ≥8 g/dL, total bilirubin ≤1.5 × ULN, ALT and AST ≤3 × ULN, serum creatinine ≤1.5 × ULN. Patients were either post-menopausal, or if premenopausal, a negative pregnancy test within 7 days of entry was required. A window of ≥15 days prior to scheduled hysterectomy was required. Patients were excluded if they were using strong or moderate CYP3A inducers, or were receiving another investigational agent. Patients with a known personal history of cardiac syncope, ventricular arrhythmia, uncontrolled hypertension, baseline grade 2 or higher diarrhea, ongoing active infection requiring treatment, and those who are pregnant or nursing were ineligible.

2.3. Statistical analysis

The primary objective was to determine the magnitude of changes in Ki-67 expression from the pretreatment specimen (e.g. biopsy or D&C) to the post-treatment hysterectomy specimen following treatment with letrozole and abemaciclib. Ki-67 expression was assessed at baseline (e.g. pre-treatment biopsy or D&C specimen), and in the tumor sample obtained during surgery (post-treatment). Evaluable patients for this endpoint were any patient who completed 2 weeks (14 days) of therapy with both study drugs and who underwent surgery (hysterectomy). A paired *t*-test was used to determine the change in Ki-67 expression.

Table 1
Baseline characteristics.

	$N = 25$
Age	62 (54, 66)
Race	
White	17 (68%)
Black	6 (24%)
More than one race	2 (8%)
Ethnicity	
Hispanic	5 (20%)
Non-Hispanic	20 (80%)
BMI	37 (30–40)
ECOG Performance Status	
0	21 (88%)
1	2 (8%)
2+	1 (4%)
Missing	1 (4%)
Menopausal Status	
Pre-menopausal	6 (24%)
Post-menopausal	19 (76%)
Stage	
I	22 (88%)
II	2 (8%)
III	0
IV	1 (4%)
Histology	
Endometrioid	25 (100%)
Grade	
Grade 1	19 (76%)
Grade 2	6 (24%)
Grade 3	0 (0%)

Data presented as n (%) for categorical variables and median (IQR) for continuous variables.

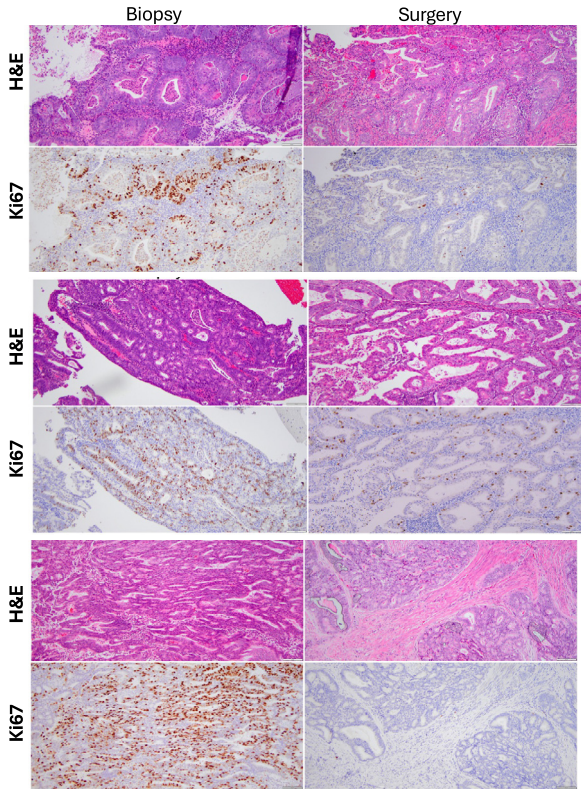

Fig. 1. Representative IHC staining for Ki67 in three individual patients' pre- and post-treatment samples. H&E staining is included for reference for each section.

Secondary endpoints included correlations between other biological characteristics of tumors (e.g. MMR status, expression of cyclin D1, p16, PTEN, and pRB) with the change in Ki-67 expression induced by the letrozole and abemaciclib combination. Evaluable patients for these endpoints were any patient who completed 80% of therapy with both study drugs followed by hysterectomy. Simple linear regression models were used to correlate continuously measured baseline biomarker expression with 2-week changes in Ki-67 expression. Unsupervised hierarchical clustering was used with dichotomous biomarker (positive/present versus negative/absent) to represent profiles across study participants. Pairwise dependence plot is based on Cramer's V, a statistical measure of association between variables, giving a value between 0 (no association) and 1 (perfect association).

Sample size was based on a reported median [IQR] Ki-67 score (% staining) 40% [24% - 52%] among 179 patients with endometrial cancer [31]. Assuming the Ki-67 scores are normally distributed, this corresponds to mean baseline scores of 40% and SD = 20%. Assuming moderate ($\rho = 0.50$)within-subject correlation between pre- and post-treatment Ki-67 scores, this also corresponds to SD = 20% for the within-subject changes in Ki-67 scores. Based on a paired t-test, a sample size of 21 would provide 80% power with two-sided $\alpha = 0.05$ to detect a 12.9% decrease in Ki-67 expression, which corresponds to a reduction from 40% staining to 27.1% staining. A 10% difference in Ki-67 staining corresponds to approximately HR = 1.3 for cancer-specific survival, and therefore the 12.9% change that we can detect with the proposed sample size would be clinically meaningful [31]. The estimated effect size was smaller and no longer statistically significant (HR = 1.14, $p = 0.26$) when adjusted for age, stage and histology, although the HR estimate may be affected by collinearity between ki67 and the adjusting variables leading us to use the HR = 1.3 for our estimates.

2.4. Immunohistochemistry (IHC)

Formalin-fixed and paraffin-embedded tissues were sectioned 4 μm in thickness. After deparaffinization and antigen retrieval, all immunohistochemical staining was performed on a Ventana Nexus automated system (Tucson, Arizona). In brief, endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Primary antibodies were detected using standard biotinylated anti-mouse or anti-rabbit secondary antibodies. Antibodies included Ki-67, p16, RB1, PTEN and CyclinD1. Immunostaining was scored by two board-certified pathologists who were masked to clinical factors. Areas of disagreement were resolved via consensus review. Immunostain for ki-67 was scored quantitatively. The Ki-67 index was the percentage of positive tumor cells from 0% to 100% (counting for 1000 cells). Immunostain for p16, pRB and Cyclin D1 were scored semiquantitatively. Intensity was scored as negative (0), weak (1+), moderate (2+), or strong (3+). Immunostains for PTEN and MSI panel were scored as positive (1 + −3+) or negative (0). The detailed antibody information and working conditions were summarized in Supplementary Table 1.

3. Results

3.1. Patient Characteristics

A total of 27 women were enrolled between October 2019 and October 2022, 2 patients withdrew consent leaving 25 evaluable patients. Demographics are listed in Table 1. The median age was 62 (IQR:

Table 2
Reduction in Ki-67.

	Mean (95% CI)
Baseline Ki-67	34 (25, 43)
Post-treatment Ki-67	14 (8, 21)
Change in Baseline Ki-67	
Mean (95% CI)	−19 (−29, −10)
Median (IQR)	−26 (−32,0)

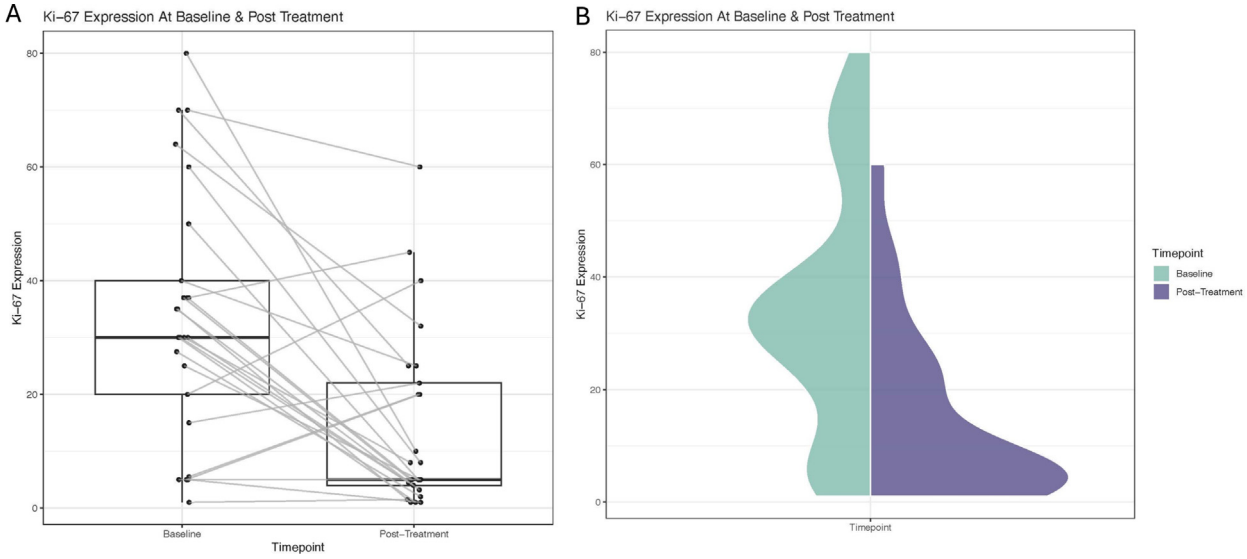

Fig. 2. Change in Ki-67 between baseline and post-treatment specimens. A) Box plots indicate Ki-67 expression at baseline and post treatment; B) Violin plot of Ki-67 expression at baseline and post treatment.

Variable	N	Ki–67 at Baseline	P–Value	Forest Plot
PTEN			0.053	
Negative	20	30.0 (20.2, 39.8)		
Positive	5	48.8 (35.4, 62.2)		
Cyclin D1			0.5	
Negative	2	20.0 (−9.4, 49.4)		
Positive	23	35.0 (25.9, 44.1)		
pRB			0.11	
Negative	8	24.8 (14.1, 35.6)		
Positive	17	38.0 (26.6, 49.3)		
P16			0.8	
Negative	2	32.5 (27.6, 37.4)		
Positive	23	33.9 (24.4, 43.3)		
MMR Presence			0.6	
All Present	14	38.0 (26.2, 49.8)		
One or More Absent	7	32.1 (14.9, 49.4)		
Unknown	4			
MLH1			0.8	
Absent	5	38.0 (16.8, 59.2)		
Present	16	35.4 (24.4, 46.5)		
Unknown	4			
PMS2			0.8	
Absent	5	38.0 (16.8, 59.2)		
Present	16	35.4 (24.4, 46.5)		
Unknown	4			
MSH2				
Absent	1	30.0 (NA, NA)		
Present	19	38.0 (28.0, 48.0)		
Unknown	5			
MSH6			0.3	
Absent	2	17.5 (−7.0, 42.0)		
Present	19	38.0 (28.0, 48.0)		
Unknown	4			

Fig. 3. Baseline Ki-67 expression, by biomarker.

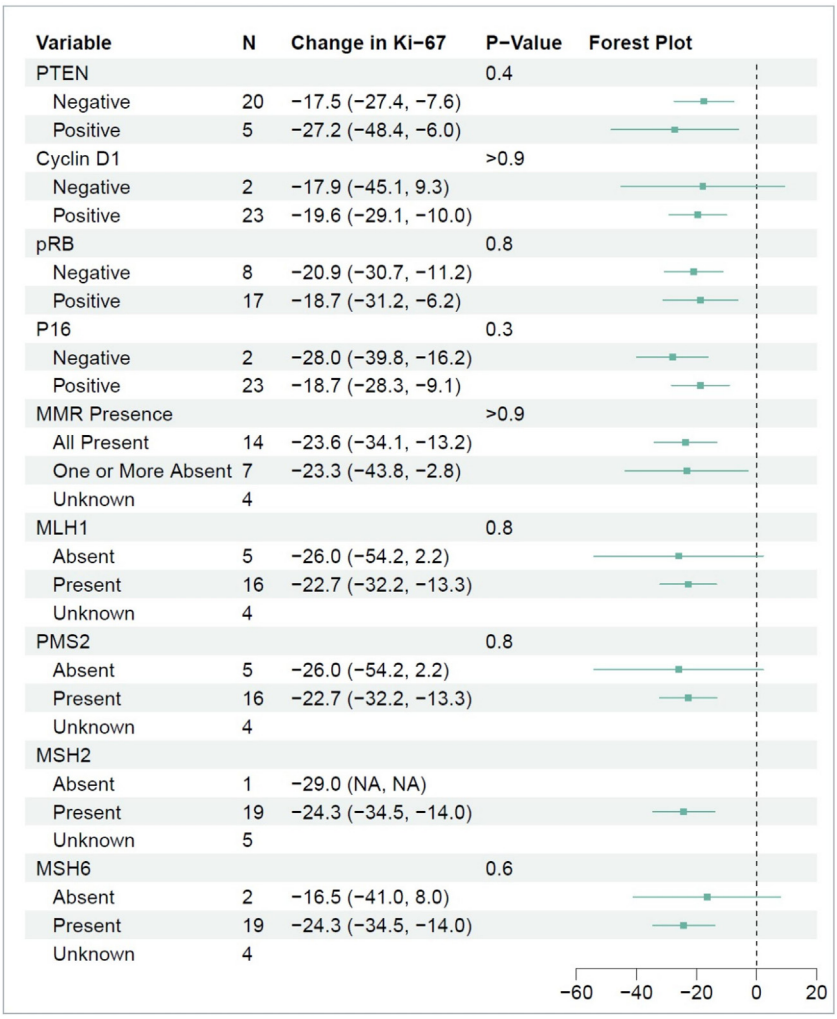

Fig. 4. Mean change in Ki-67 expression, by biomarker.

54–66) and 19 patients (76%) were post-menopausal. Most patients were White (68%), 24% identified as Black; 20% were of Hispanic ethnicity. Median BMI was 37 (IQR: 30–40). All cancers were low grade endometrioid with the majority being FIGO grade 1 (76%) and the remainder (24%) grade 2. Seven (28%) patients had mismatch repair deficient tumors. Twenty-two (88%) patients were stage I, two (8%) stage II, and 1 (4%) stage IV.

3.2. Efficacy

The mean baseline Ki-67 was 34% (SD 22%). After 2 weeks of treatment with abemaciclib and letrozole (mean duration 13.4 days, SD 2.0), the mean Ki-67 was 14% (SD 16%). Representative staining for Ki-67 in pre-treatment biopsies and post-treatment surgical specimens is shown in Fig. 1. The mean absolute reduction in Ki-67 was 19% (SD 23%, $p < 0.001$), which represents greater than 40% relative reduction in the proliferative index. This level of inhibition met the prespecified endpoint, indicating a clinically meaningful reduction in cell proliferation induced by this combination (Table 2 and Fig. 2A-B).

3.3. Toxicity

There were no serious adverse events recorded. All patients completed the 2-week drug treatment with no discontinuations. The most common study related adverse events were grade 1–2 diarrhea (68%) and grade 1–2 nausea (36%). Two patients had grade 3 hematological events (anemia and neutropenia), which resolved. Importantly, there were no adverse events that delayed surgery, demonstrating feasibility of the approach in a window of opportunity setting.

3.4. Correlative analyses

Tumor sections were assessed for expression of MMR related proteins, cyclin D1, PTEN, p16, and phospho RB. In this cohort, 20 of 25 (80%) tumors had absent PTEN, 7 (28%) were MMR deficient, and 8 (32%) were phospho-RB negative. Most tumors stained positively for p16 (23 of 26) and for cyclin D1 (23 of 25, Fig. 3). There were no significant differences in baseline Ki-67 expression based on present or absent staining for pRb, cyclin D1, p16, or MMR proteins (Fig. 3). There were also no significant differences in the magnitude of Ki-67 reduction based upon present or absent staining for pRb, cyclin D1, p16, or MMR proteins (Fig. 4). Baseline Ki-67 was moderately associated with positive staining for PTEN (Fig. 3, $p = 0.05$). Post-menopausal patients had a mean decrease in Ki-67 of 22% compared to 10% for those who were premenopausal (Fig. 4), but this did not reach statistical significance ($p = 0.3$). Correlations between biomarkers expressed in the same patient were performed and did not reveal any significant co-expression patterns (Supplementary Fig. 1).

4. Conclusions and discussion

Abemaciclib and letrozole induced a reduction in cellular proliferation in endometrioid endometrial cancer over a relatively short two-week period prior to surgery. These findings provide evidence that short-term neoadjuvant therapy prior to surgery can result in significant changes in tumor biology. The observed decrease in Ki-67 reflects a potent anti-proliferative effect of this combination, supporting further clinical evaluation.

A limited number of surgical window of opportunity studies have been undertaken for endometrial cancer and provide opportunity for comparison to the results observed in our study [32–34]. A reduction of 20% in Ki-67 was found in a recent study of megestrol acetate alone [32]. Decrease of 12.9% in Ki-67 was recorded in a randomized trial of metformin versus no medication [33]. The observed 19% decrease in mean Ki-67 expression in our study compares favorably with these results and suggests that this combination could have efficacy similar to other currently used hormonal treatments for endometrioid endometrial cancer such as megestrol acetate.

There is significant interest in developing this combination for treatment of NSMP endometrial cancer. Recent single arm phase II studies testing abemaciclib and letrozole in metastatic endometrial cancer reported response rates of 30–44% [29,30]. A randomized phase II trial of palbociclib and letrozole compared with placebo and letrozole among patients with measurable metastatic endometrioid cancer found an improved PFS among those receiving CDK4/6 inhibition (8.3 months versus 3.1 months) [35]. The ongoing GOG-3039 phase II study of abemaciclib and letrozole for advanced recurrent or metastatic endometrial cancer will provide definitive evidence regarding the efficacy of this combination for advanced metastatic endometrial cancer [36].

Compared to previously reported therapeutic trials testing aromatase inhibitors with CDK4/6 inhibitors, we found a lower rate of grade 3 AEs (8%, all cytopenias), likely due to the short course of therapy and to the fact that patients enrolled in this trial did not receive previous chemotherapy. Notably, none of the observed adverse events altered the surgical schedule or surgical outcome for these patients, supporting feasibility of such research interventions in the pre-surgical setting.

Our study has several limitations. All patients in this study had grade 1 or 2 estrogen receptor positive endometrioid cancers; therefore results are not generalizable to high grade cancers. As this was a surgical window of opportunity study, the biological endpoints do not confirm clinically efficacy of this combination. Additionally, the effects of individual agents in this combination cannot be determined from this study design. The preplanned subgroup analyses to correlate the decrease in Ki-67 staining with the presence of absence of pRb, cyclin D1, p16 and MMR proteins did not identify significant associations. This is likely due to the small sample size as the trial was not powered for these comparisons. The trial did not exclude pre-menopausal women, even though the effects of AIs are limited in this setting. Only a few pre-menopausal women were enrolled and the magnitude of Ki67 decrease in this population was lower than in post-menopausal patients. Finally, due to funding limitations we were unable to perform genomic sequencing. However, our results provide important information about low grade endometrial cancers and the direct biological effects of abemaciclib and letrozole on cellular proliferation in this setting.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2026.07.001.

CRediT authorship contribution statement

Emma L. Barber: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jian-Jun Wei:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis. **Amanda L. Strickland:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis. **John W. Moroney:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation. **Dario R. Roque:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Edward J. Tanner:** Writing – review & editing, Resources, Methodology, Investigation. **Jonathan Parker:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Katrina Dobinda:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Maxwell Shramuk:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Masha Kocherginsky:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation. **Daniela Matei:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors report funding for this investigator-initiated trial provided by Eli Lilly to Dr. Barber's institution. Drs Barber, Wei, Moroney, Tanner, and Kocherginsky; and Mr. Parker report no conflicts of interest. Dr. Strickland reports consulting payments from Abbive unrelated to this work. Dr. Roque received consulting payments from Merck, GlaxoSmithKline, Intuitive Surgical, and Abbvie unrelated to this work. Dr. Matei reports receiving consulting payments from CVS Health, GSK, Corcept Inc. unrelated to this work.

Acknowledgements

Funding for this investigator-initiated trial was provided by Eli Lilly. Career development funding was provided to Dr. Barber by the NICHD (K12 HD050121) and the GOG Foundation. This work was supported by the Robert H Lurie Comprehensive Cancer Center Clinical Trials Office and Quantitative Data Sciences Core (NCI CCSG P30 CA060553).

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