

ORIGINAL RESEARCH

OATH trial: a phase II trial evaluating the combination of onapristone with anastrozole for women with hormone receptor positive endometrial cancer

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Abstract

Background: The phase II Onapristone with Anastrozole for the Treatment of Hormone-receptor positive endometrial cancer (OATH) study aimed to evaluate the activity and safety of onapristone, a type 1 anti-progestin, in combination with anastrozole in patients with recurrent or metastatic hormone receptor positive endometrial cancer. The co-primary endpoints were objective response rate using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria and progression-free survival. Secondary endpoints included disease control rate, duration of response, safety and tolerability, and quality of life assessments. **Methods:** This multicenter, open-label, prospective single-arm, phase II trial enrolled patients with hormone receptor positive (estrogen or progesterone receptor >1%) recurrent or metastatic endometrial cancer to receive onapristone 50 mg twice daily with anastrozole 1 mg once daily until disease progression or unacceptable toxicity. **Results:** As of December 2024, 14 patients were enrolled, with 13 patients evaluable for at least one tumor assessment after baseline. One patient achieved a complete response, 2 patients achieved a partial response, 10 patients had stable disease, and one patient had progressive disease. The overall response rate was 21.4%, and the median progression-free survival was 14.2 months. The disease control rate was 92.9%. The duration of response for the patient with a complete response was 26.7 months, and the duration of response for the patients with partial responses was 23 and 6.5 months, respectively. The most common adverse events were grade 1 or 2 vasomotor symptoms (36%), transaminitis (29%), nausea (29%), and diarrhea (23%). No grade 4 adverse events or treatment-related deaths were observed. **Conclusions:** Onapristone combined with anastrozole in patients with pretreated, recurrent, or metastatic hormone receptor positive endometrial cancer shows promising activity in preliminary phase II results. Treatment is well-tolerated and offers a plausible therapeutic alternative for mismatch repair-proficient endometrial cancer patients with recurrent or metastatic disease. **Clinical Trial Registration:** NCT04719273.

Keywords

Endometrial cancer; Hormone receptor positive; Hormonal therapy; Uterine cancer

1. Introduction

Endometrial cancer is the most common gynecologic cancer and one of the leading causes of cancer-related death among American women [1]. Advanced-stage endometrial cancer is primarily treated with chemotherapy with or without immunotherapy. Patients with advanced endometrial cancer are often initially treated with platinum-based chemotherapy, and many endometrial cancers express hormone receptors and may respond to hormone-directed therapy. Upon disease recurrence or metastasis, endometrial cancer patients are often treated with chemotherapy or combination therapy regimens, which

can lead to significant side effects and can impair quality of life. The past decade has witnessed significant progress in therapeutic development for endometrial cancer, specifically utilizing chemoimmunotherapy and antiangiogenic agents [2]. Despite these advancements, most patients with recurrent or metastatic endometrial cancer have limited treatment options with a 4 to 27% response rate to conventional chemotherapy [2]. Therefore, the development of second-line therapies that result in improved response is an unmet clinical need [3]. Using targeted hormonal treatment may present potential opportunities for improved treatment outcomes for these women.

In pursuit of effective and tolerable therapeutic opportunities

for patients with recurrent or metastatic hormone receptor positive endometrial cancer, spanning both previously heavily treated and treatment-naïve patients, hormonal therapies have been utilized with objective response rates between 9–24% [4–6]. Megestrol acetate is approved in the recurrent or metastatic setting and has shown response rates as high as 24% in conjunction with tamoxifen, however, its use is limited due to poor tolerance [4, 5]. Additionally, aromatase inhibition with anastrozole in the recurrent or metastatic setting results in a 9% response rate [6]. These low to moderate response rates underscores the imperative for new treatment options that are both effective and tolerable for patients [7]. As such, hormonal therapy has been used in combination with other therapies, including mammalian target of rapamycin (mTOR) inhibition, in the recurrent or metastatic setting [8–10]. However, there remains a need for additional combination therapies that may target hormone receptor positive recurrent or metastatic endometrial cancer.

Onapristone is a well-tolerated, oral, full type 1 progesterone antagonist and has shown promising preliminary findings in gynecologic cancers. Both progesterone receptor isoforms, PRA and PRB, have been detected in endometrial cancers [11]; onapristone prevents dimerization of the PRA and PRB monomers, inhibits ligand-induced phosphorylation and prevents association of the progesterone receptor with its co-activators, thus preventing progesterone receptor-mediated DNA transcription. Preclinical efficacy across various *in vivo* models heralds it as a potential therapeutic option in breast cancer [12]. Phase 1 dose-escalation outcomes utilizing single-agent onapristone reveal a desirable safety profile with a combined best response (partial response and stable disease greater than or equal to 24 weeks) in 2 out of 13 heavily pretreated uterine endometrioid cancer patients (15%) [13]. This phase 1 dose-escalation trial of onapristone demonstrated a well-tolerated and meaningful clinical option in progesterone-receptor positive endometrial cancer patients.

The biological plausibility of the synergistic effect of utilizing of combination hormonal therapies with onapristone could lead to the induction of terminal differentiation, leading to cellular death. Pre-clinical and early phase studies have suggested safety and enhanced anti-tumor effects of onapristone when combined with pure anti-estrogens, anti-estrogens with partial estrogenic activity (tamoxifen), androgen biosynthesis inhibitors or aromatase inhibitors in endometrial, ovarian breast and prostate cancer [14–16]. The combination of aromatase inhibition to reduce estrogen production with progesterone blockade production with onapristone has particular biologic implications in endometrial cancers. The combination of onapristone (type 1 progesterone antagonist) with anastrozole (aromatase inhibitor) has yet to be studied in the context of recurrent or metastatic endometrial cancer. Leveraging these insights to address this unmet need, the OATH phase II clinical trial was designed to assess the therapeutic efficacy and safety of onapristone in combination with anastrozole in the treatment of patients with recurrent or metastatic hormone receptor-positive endometrial cancer.

2. Methods

2.1 Study design and participants

This multicenter, prospective, open-label, single-arm phase II trial evaluated patients with recurrent or metastatic endometrial cancer characterized by hormone receptor positivity. Patients with estrogen receptor (ER)/progesterone receptor (PR) positivity ($\geq 1\%$ by immunohistochemistry) with recurrent, locally advanced, or metastatic endometrial cancer received onapristone extended-release 50 mg orally twice daily in combination with anastrozole 1 mg orally once daily until disease progression or unacceptable toxicity.

Eligibility criteria included being 18 years or older, histologically confirmed diagnosis of endometrial cancer with estrogen receptor and/or progesterone receptor expression $\geq 1\%$ by immunohistochemistry; patients having received or not received prior chemotherapy with a maximum of up to 2 prior lines of therapy allowed; measurable disease as defined by RECIST v1.1 (of at least one lesion that can be accurately measured in at least one dimension); Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and adequate organ function. Key exclusionary criteria included concurrent therapies requiring at least a 3-week washout; previous hormonal-based therapy would have been completed at least 2 months prior. Subjects with carcinosarcoma histology were excluded. Ethical approval for the study was secured from the Ethics Committees of all participating centers. All participants provided written informed consent. The trial has been registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: NCT04719273).

2.2 Procedure

Participants were administered onapristone extended-release 50 mg orally twice daily in combination with anastrozole 1 mg orally once daily until disease progression or the emergence of intolerable toxicity. Dose modifications and delays due to adverse events were permitted, encompassing reductions to 30 mg orally twice daily and further to 10 mg orally twice daily. Treatment would be discontinued if the severity of adverse events required doses below 10 mg twice daily. Dose increases were prohibited. Participants who discontinued treatment for over 28 days were withdrawn from the study. Concomitant medications that inhibited or induced cytochrome P450 CYP3A4 were restricted; patients on the oral anticoagulant warfarin were recommended to have regular international normalized ratio (INR) monitoring while on study treatment.

Efficacy assessments were carried out by investigators in accordance with the RECIST version 1.1. These evaluations were conducted every 8 weeks during the first 4 months of study, and every 12 weeks thereafter until disease progression, the commencement of another antitumor therapy, or withdrawal from trial. Participants removed from study for any other event other than disease progression, or those without disease progression at the end of the treatment study period, underwent survival follow-up every 3 months by phone call or chart review. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Safety assessments encompassed adverse event monitoring, performance status, lab-

oratory tests, concomitant medication monitoring, vital signs, Edmonton symptom assessment, pill diary with recording of therapy compliance, and physical examinations.

Immunohistochemical testing of ER and PR expression as well as standard-of-care comprehensive next-generation sequencing (NGS) was used. Immunohistochemistry was performed internally at Thomas Jefferson University and Abington Jefferson Health and was standardized across the Jefferson enterprise Pathology Department. Results derived from tissue and blood samples were sourced from facilities certified by the Clinical Laboratory Improvement Amendments (CLIA) or the College of American Pathologists (CAP).

2.3 End points

The primary endpoints of this study were overall response rate (ORR) and median progression-free survival. The overall response rate was defined as the percentage of participants who achieved either a complete response or a confirmed partial response as defined by RECIST v1.1. Progression-free survival was defined as a binary endpoint, from the first dose of onapristone and anastrozole to the date of first documented disease progression or recurrence, as assessed by RECIST v1.1 criteria, or death due to any cause, whichever occurred first. Secondary endpoint included the disease control rate, duration of response, safety and tolerability and quality of life. Disease control rate was defined by best overall response of complete response, partial response or stable disease lasting for ≥24 weeks, per RECIST v1.1. Duration of response was defined as time between first date of documented response to progression or death due to endometrial cancer. Safety and tolerability were defined as the type, frequency and severity of adverse events and laboratory abnormalities, per CTCAE v5.0. Quality of life and pain were evaluated using the Edmonton Symptom Assessment System (ESAS), which includes nine subjective patient measures of well-being, including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath, and were used during each visit. Changes in values correlated with changes in quality of life.

2.4 Statistical analysis

The study design included a sample size of 25 evaluable patients with hormone receptor endometrial cancer receiving onapristone twice daily with anastrozole once daily to confidently reject the null hypothesis that the overall response rate was 15% or lower. This calculation was based on achieving an 86.9% power to detect an actual overall response rate of 40%, using a two-sided exact test at 5% level of significance.

The full analysis set included all participants who had undergone baseline tumor assessment and received at least one week of treatment with onapristone and anastrozole, with efficacy evaluations derived from this set.

Statistical analyses were executed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA). The overall response rate, progression-free survival, disease control rate, and their 95% confidence intervals (CIs) were determined using the application R [17]. Descriptive statistics, including means, medians, standard deviations, interquartile ranges (IQR), and percentages, derived from the Ed-

monton Symptom Assessment System, were calculated using R [17, 18].

2.5 Trial oversight

The study was approved by the institutional review board at each participating site and conducted in compliance with the ethical principles of the Declaration of Helsinki; the International Council for Harmonisation Consolidated Guideline E6 for Good Clinical Practice; and applicable US, European, and Japanese regulatory requirements.

3. Results

Between January 2021 and March 2023, a total of 18 patients were screened across two sites at the Sidney Kimmel Comprehensive Cancer Center at Thomas Jefferson University and Asplundh Cancer Center at Jefferson Health in the United States. 14 patients were enrolled in the trial. Up to the data cutoff of 30 November 2024, data from 14 patients were included in the full analysis set. The most common reason for treatment discontinuation was disease progression; however, the study was ultimately stopped due to a lack of access to onapristone provided by the study sponsor.

Baseline demographics and disease characteristics are summarized in Table 1. The median age was 67 years (44–80). Ten of fourteen patients were Caucasian, and four were African American; all subjects identified as not Hispanic or Latino. Most participants had an ECOG performance status of 1 (64%); while 29% had an ECOG performance status of 2. All patients received at least 1 previous line of systemic therapy (chemotherapy and/or immunotherapy) (91%); this includes prior chemotherapy (91%) and prior immunotherapy (21%). 50% of patients had received prior radiation. Patients were allowed to participate if they had received prior hormonal therapy, but they were not allowed to utilize hormonal therapy within 2 months prior to enrollment. The median duration of study treatment was 4.2 months with a range of 1.0 to 19.9 months (Table 1).

TABLE 1. Patient demographics.

Demographic	Number (n = 14)
Age (yr, median)	67 (44–80)
Performance Status	
0	5 (36%)
1	9 (64%)
Prior lines of chemotherapy	
0	1 (7%)
1	9 (64%)
2	4 (29%)
Prior radiation	7 (50%)
Prior immunotherapy	3 (21%)
Median treatment duration (mon)	4.2 (1.0–19.9)

The efficacy analyses included all 14 evaluable patients. The results by investigator review revealed the confirmed overall response rate was 21.4% (95% CI: 4.7%, to 50.8%), and the median progression-free survival of 14.2 months (95% CI: 9.6 months to not applicable (NA)) (see Fig. 1). The best clinical response that was demonstrated in these patients included one complete response (7.1%), two partial responses (14.3%), ten patients with stable disease (71.4%), and one patient had progressive disease (7.1%) (Table 2). The disease control rate was 92.9% (95% CI: 66.1%, 99.8%). The patient who achieved a complete response has maintained a sustained response for 26.7 months after starting treatment, which continues at the time of data analysis. The patients with partial response sustained response for 23 months and 6.5 months, respectively, prior to progression of disease (Fig. 2). Baseline estrogen and progesterone receptor tumor membrane expression by immunohistochemistry was variable (Table 3). The estrogen receptor ranged from 5%–100%, the progesterone receptor ranged from 1%–100%. In the two patients with response, the patient with partial responses had 55%–100% estrogen receptor, 91%–100% progesterone status, and the patient with complete response had 100% estrogen receptor, 100% progesterone receptor expression on immunohistochemistry (Fig. 3). Molecular subtypes were recorded for all patients based on commercial next-generation sequencing results and are recorded in Table 3. For patients with stable disease, the mean time to progression was 34.9 weeks (median 39.1 weeks) with a range of 15 to 100 weeks.

Safety data demonstrated the most common adverse events were grade 1 or 2, including vasomotor symptoms (36%), an increase in alanine aminotransferase or aspartate aminotrans-

TABLE 2. Best overall response to treatment.

Name	Count	Percentage	95% Two-Sided Exact Confidence Interval
PD	1/14	7.1%	(0.2%, 33.9%)
SD	10/14	71.4%	(41.9%, 91.6%)
PR	2/14	14.3%	(1.8%, 42.8%)
CR	1/14	7.1%	(0.2%, 33.9%)
ORR	3/14	21.4%	(4.7%, 50.8%)
DCR	13/14	92.9%	(66.1%, 99.8%)

PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response; ORR: Overall Response Rate; DCR: Disease Control Rate.

ferase (29%), nausea (29%), and diarrhea (23%) (Fig. 4). No grade 4 adverse events occurred. One subject ultimately had a treatment discontinuation of onapristone due to transaminitis but remained on anastrozole. No treatment related deaths were observed.

Self-reported quality of life measures were assessed by the Edmonton Symptom Assessment in 12 of 14 patients. The main patient-reported quality of life adverse events included psychosocial (anxiety, depression, well-being), neurologic, endocrinologic (hot flashes), musculoskeletal (arthralgias), gastrointestinal (nausea/vomiting), pain, and tiredness. Additionally, less commonly reported self-reported quality of life adverse events were observed. Table 4 includes quantitative analysis of change-from-baseline analyses on the Edmonton Symptom Assessment.

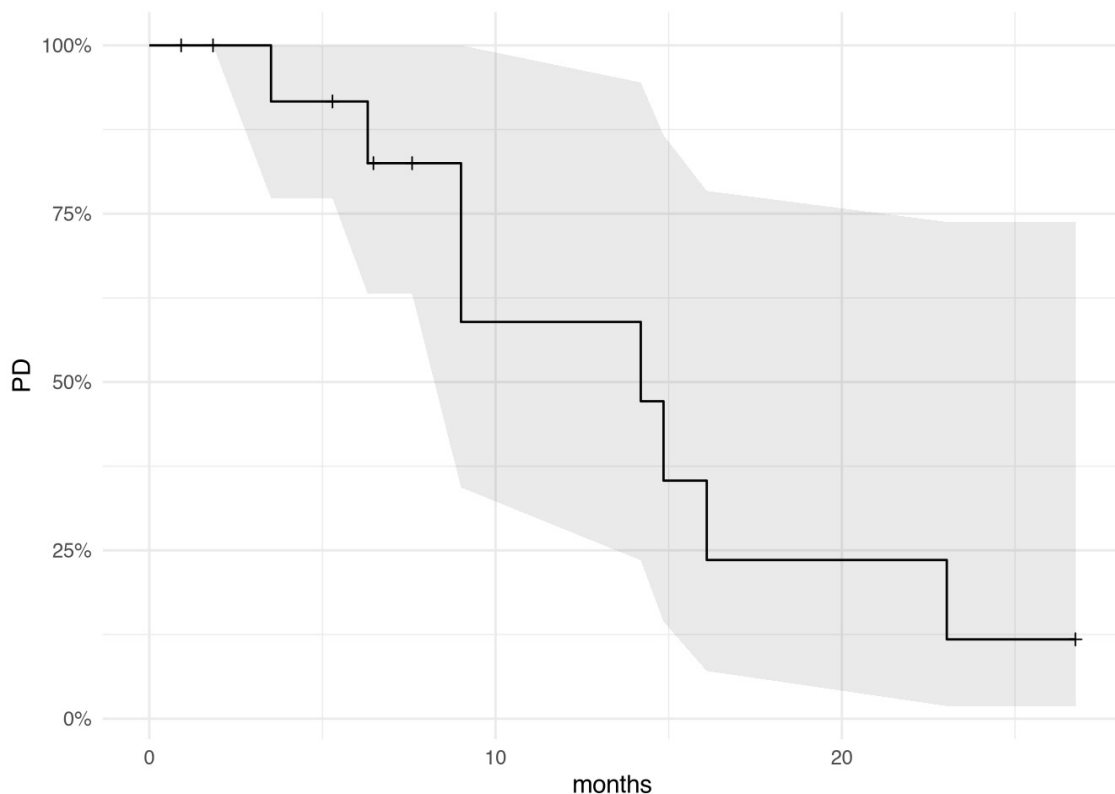


FIGURE 1. Kaplan-Meier curve of progression free survival. PD: Progressive Disease.

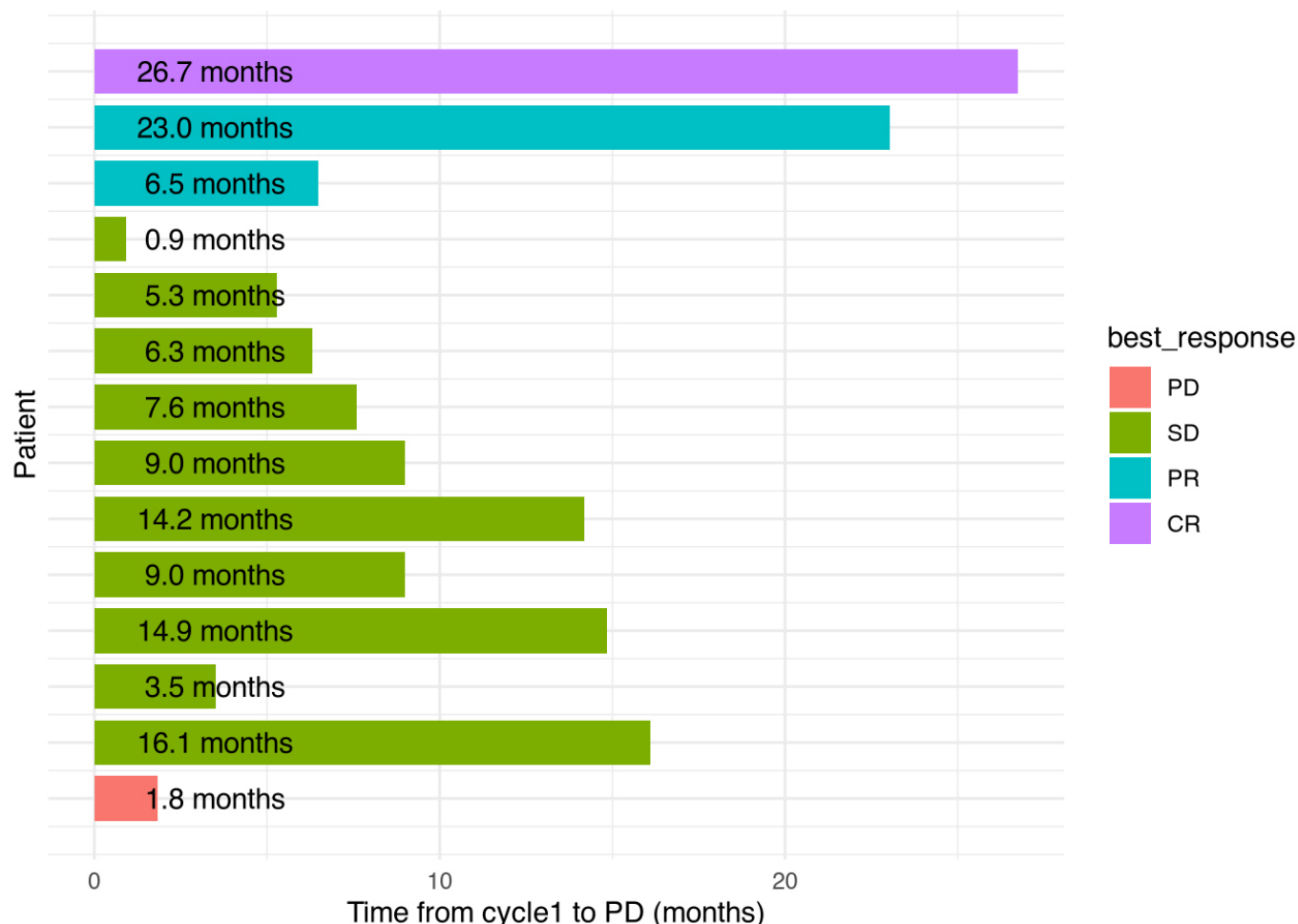


FIGURE 2. Best disease response by time. PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response.

4. Discussion

Here, we report the final activity and tolerability results from the OATH study in recurrent or metastatic hormone-receptor-positive endometrial cancer. In the current landscape of hormone-receptor-positive endometrial cancer, it is crucial to have durable therapeutic options with a favorable safety profile. The combination of onapristone and anastrozole provides a promising and tolerable therapeutic opportunity for endometrial cancer patients, particularly for those who were previously treated. Onapristone and anastrozole demonstrated a median duration of treatment of 4.2 months, with a maximum of up to 19.9 months at the time of data cut-off. This result was higher than previously reported outcomes for single-agent hormone-based therapy, including the previous data on utilizing single-agent onapristone [12]. The disease control rate in the OATH study was 92.9%, suggesting a therapeutic option that has the potential for sustained response. Patients on study with stable disease demonstrated stability for prolonged duration with a mean of 34.9 weeks (8.7 months), with one subject reaching 100 weeks (25 months) of stable disease. This suggests that the progression-free survival data was not skewed by the one complete and one partial responder. The response and disease control rates were irrespective of prior therapies. All patients

had received prior local or systemic therapy, such as radiation therapy or chemotherapy; 13 out of 14 patients had received prior chemotherapies. Four of the patients (29%) had received two lines of prior chemotherapy, and 3 patients (21%) had received prior immunotherapy. This study, therefore, suggests a promising agent that is chemotherapy-sparing in recurrent or metastatic hormone-receptor-positive patients.

Disease response was observed across all histologic subtypes. Molecular profiling demonstrates significant complexity and heterogeneity, as outlined in Table 3, including subjects with aggressive molecular alterations with known endocrine and chemotherapy resistance. Of the 13 patients with comprehensive genomic sequencing performed, clinical response to onapristone and anastrozole was observed despite significant molecular heterogeneity in our population. Notably, half of the subjects had mutations in phosphatase and tensin homolog (PTEN), six patients had mutations in the phosphatidylinositol-4,5-bisphosphonate 3-kinase (PIK3) pathway, five patients had mutations in AT-rich interaction domain 1A (ARID1A), two patients had mutations in Cyclin E1 (CCNE1), and two patients were mismatch repair deficient (dMMR). Despite known resistance mechanisms to hormonal blockade in the above mutations, many subjects demonstrated clinical benefit on onapristone and anastrozole. Therefore, more preclinical and clinical data are needed to elucidate the biologic interplay between

TABLE 3. Histologic and molecular specifications with disease response.

Subject	Histology	Molecular Alterations (Next Generation Sequencing)	Estrogen Receptor/Progesterone Receptor%	Best Clinical Response	Time to Progression (d)
1	Endometrioid	dMMR/MSI-h, ARID1A, CTNNB1, PIK3CA, ASXL1, BCL9, CTCF, FGFR2, KDM6A, KMT2A, NRAS, NSD1	60%/2%	Stable Disease	490
2	Adenocarcinoma, NOS	Not performed	100%/100%	Complete Response	N/A
3	Serous	PPP2R1A, TP53C135S, ERBB2 amp (HER2 3+ on FISH)	30%/0%	Stable Disease	106
4	Endometrioid	ARID1A, CTNNB1, PIK3R1, PTEN, BCOR	95%/95%	Stable Disease	452
5	Endometrioid with squamous differentiation	ARID1A, DICER1, KRAS, PIK3CA, PTEN, WRN	10%/10%	Stable Disease	56
6	Endometrioid	ESR1, PIK3R1, PTEN, TP53	100%/100%	Stable Disease	274
7	Endometrioid	dMMR	95%/80%	Stable Disease	67
8	Endometrioid	ARID1A, PTEN, CTNNB1	55%/95%	Partial Response	197
9	Endometrioid	CTNNB1, PIK3CA, PTEN, BCOR	100%/100%	Partial Response	701
10	Serous	ERCC1	95%/5%	Stable Disease	274
11	Endometrioid	CTNNB1, PIK3CA, PIK3R1, PTEN	5%/20%	Stable Disease	194
12	Endometrioid with squamous differentiation	ARID1A, CTNNB1, PIK3CA, PTEN	95%/95%	Stable Disease	194
13	Serous	CCNE1, MEN1, NF1, TP53	75%/25%	Stable Disease	161
14	Serous	BCL2, CCNE1, CRKL amp, MAPK, TP53	Unknown+	Progressive Disease	28

dMMR: Mismatch repair deficient; ARID1A: AT-rich interaction domain 1A; CTNNB1: Catenin beta-1; PIK3: Phosphatidylinositol-4,5-bisphosphate 3-kinase; ASXL1: additional sex combs like 1; BCL9: B-cell lymphoma 9; FGFR2: Fibroblast Growth Factor Receptor 2; KDM6A: Lysine-specific demethylase 6A; KMT2A: Histone-lysine-N-methyltransferase 2A; NRAS: Neuroblastoma rat sarcoma virus; NSD1: nuclear receptor binding SET domain 1; PPP2R1A: serine/threonine-protein phosphatase 2A; ERBB2: erythroblastic oncogene B; PTEN: Phosphatase and Tensin homolog; BCOR: BCL6 Corepressor; WRN: werner helicase; KRAS: Kirsten rat sarcoma virus; ESR1: estrogen receptor 1; CCNE1: Cyclin E1; MEN1: multiple endocrine neoplasia 1; NF1: neurofibromatosis 1; CRKL: chicken tumor virus 10 regulator of kinase-like; MAPK: mitogen-activated protein kinase; MSI-h: microsatellite instability high; CTCF: CCCTC-binding factor; HER: Human Epidermal growth Receptor; FISH: Fluorescence In-situ Hybridization; TP53: tumor protein 53; ERCC1: excision repair cross-complementation group 1; NOS: Not otherwise specified; N/A: not applicable; amp: amplified.

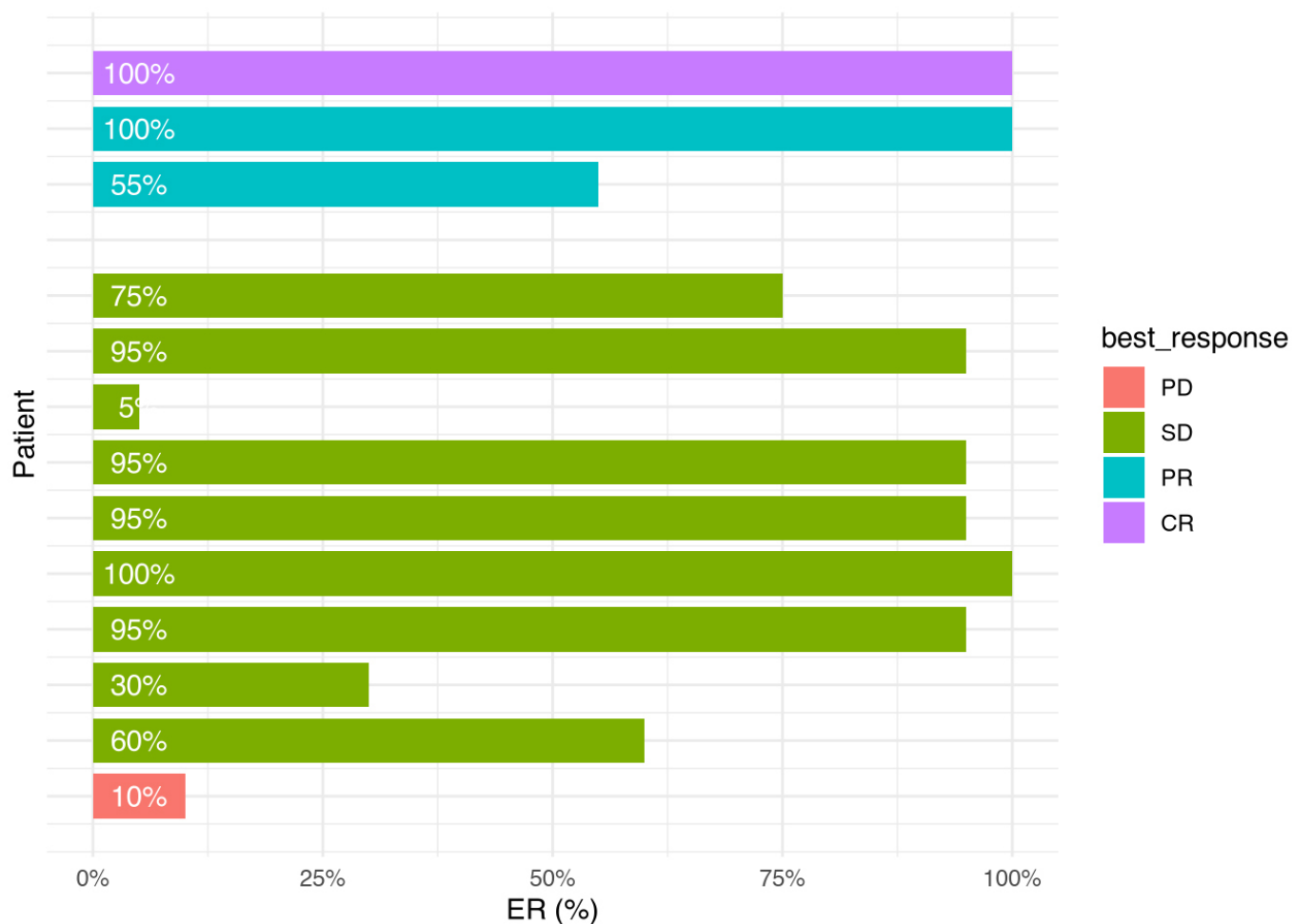


FIGURE 3. Disease response with relation to ER% positivity. PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; CR: Complete Response; ER: Estrogen Receptor.

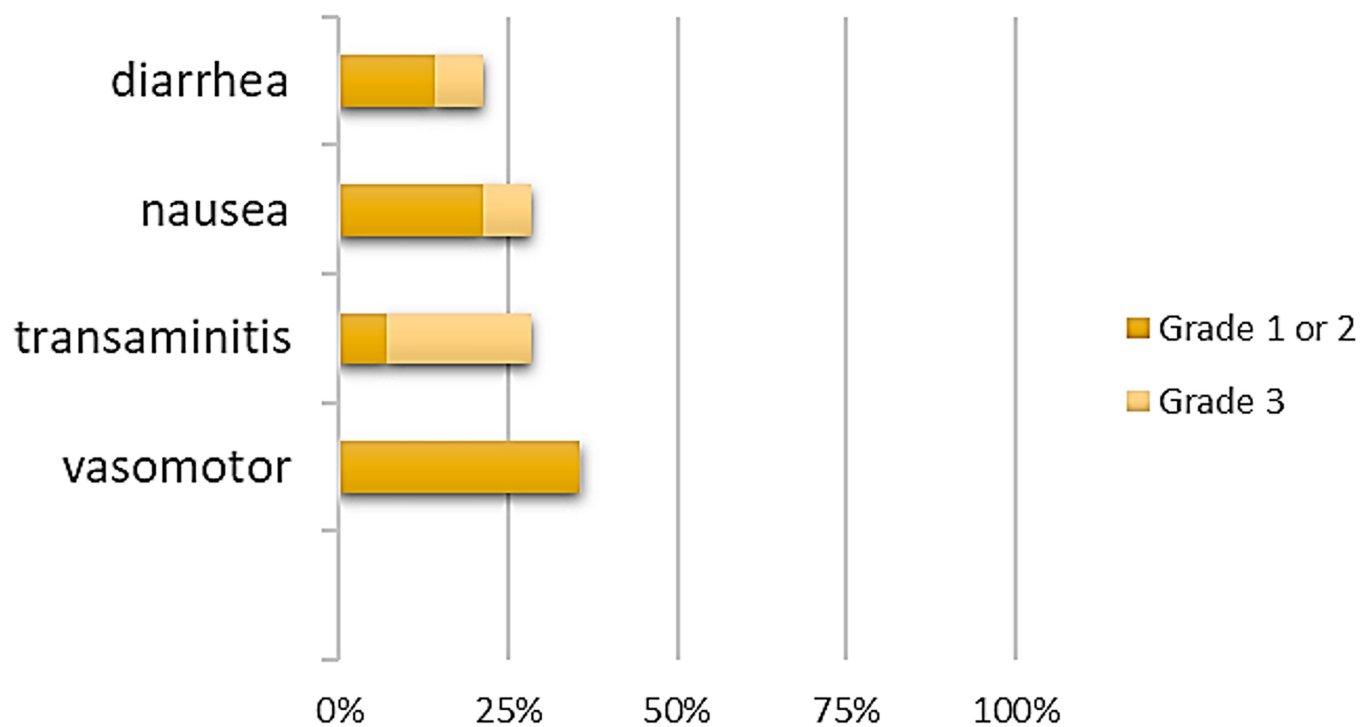


FIGURE 4. Investigator-reported adverse events.

TABLE 4. Patient reported adverse events by Edmonton symptom assessment.

	Baseline (n = 12) (mean ± standard deviation)	Grade 1 (n = 5) (mean ± standard deviation)	Grade 2 (n = 1) (mean ± standard deviation)	Grade 3 (n = 6) (mean ± standard deviation)	Significance (1 level(s) of single obs omitted, Wilcoxon- Mann-Whitney)
Anxiety	1.3 ± 1.1 (0.0–3.1)	1.0 ± 0.9 (0.0–1.7)	2.5 (sd = 0)	1.3 ± 1.3 (0.0–3.1)	0.782
Change in Appetite	2.4 ± 1.9 (0.0–4.8)	1.1 ± 1.8 (0.0–4.0)	3.8 (sd = 0)	3.3 ± 1.6 (0.6–4.8)	0.053
Depression	1.1 ± 1.1 (0.0–2.7)	1.0 ± 0.9 (0.0–1.7)	2.5 (sd = 0)	1.1 ± 1.2 (0.0–2.7)	0.926
Drowsiness	1.5 ± 1.6 (0.0–4.5)	1.2 ± 1.9 (0.0–4.5)	2.8 (sd = 0)	1.4 ± 1.5 (0.0–4.2)	0.645
Nausea	1.0 ± 1.5 (0.0–3.7)	0.9 ± 1.6 (0.0–3.7)	0.9 (sd = 0)	1.2 ± 1.6 (0.0–3.5)	0.575
Pain	2.2 ± 2.2 (0.0–5.7)	1.2 ± 1.6 (0.0–3.5)	0.8 (sd = 0)	3.3 ± 2.3 (0.2–5.7)	0.114 (Two-Sample <i>t</i>)
Shortness of breath	0.9 ± 1.5 (0.0–4.1)	0.1 ± 0.2 (0.0–0.5)	0.5 (sd = 0)	1.6 ± 1.8 (0.0–4.1)	0.245
Tiredness	3.2 ± 2.6 (0.0–7.5)	1.9 ± 2.2 (0.0–5.3)	3.3 (sd = 0)	4.2 ± 2.8 (0.2–7.5)	0.165 (Two-Sample <i>t</i>)
Wellbeing	2.5 ± 1.9 (0.0–5.6)	1.8 ± 1.9 (0.0–3.9)	3.2 (sd = 0)	2.9 ± 2.1 (0.5–5.6)	0.399 (Two-Sample <i>t</i>)

sd: standard deviation; *obs*: observation.

these pathway alterations and response to onapristone and anastrozole. Ultimately, partial response and stable disease were noted in patients with complex molecular alterations and various histologic subtypes, suggesting that hormonal therapy is a feasible consideration for patients with hormone-receptor-positive endometrial cancer.

The adverse event profile was manageable, suggesting that the combination of onapristone and anastrozole was feasible and tolerable for patients without additive toxicity. The most common adverse events noted were vasomotor symptoms, nausea, and diarrhea, which can be managed with pharmacotherapy and other commonly used interventions, which is like the rates seen in single-agent hormone-based therapy. There was no grade 4 adverse event and no serious adverse event noted during the study. No patients suffered treatment-related discontinuations, and no deaths were observed during this study. In comparison to other potential cytotoxic therapeutic options in the recurrent or metastatic setting for endometrial cancer, this combination offers a more feasible safety profile.

Limitations to the OATH trial include that this study was halted early due to a lack of ability to obtain onapristone from the company due to funding reasons. This unfortunately limited the patient sample size to add statistical power to our analysis, and the study was unable to fulfill its sample size goal of 25 patients. Additionally, this trial enrollment occurred prior to the approval of frontline chemoimmunotherapy, which is currently the standard of care for locally advanced, recurrent, or metastatic endometrial cancer [19–21]. Subsequently, only three patients had received prior immunotherapy in this patient cohort. While the therapeutic landscape of endometrial cancer is rapidly evolving with novel therapeutic targets such as antibody-drug conjugates [22], bispecific T-cell engagers, and others, the utilization of onapristone and anastrozole affords a potential therapeutic opportunity with a favorable toxicity profile.

Future directions in developmental therapeutics could include utilizing progesterone antagonism with aromatase

inhibition in larger prospective clinical trials randomized to standard-of-care hormonal therapy. This study also suggests that comprehensive molecular testing for patients with hormone-receptor-positive endometrial cancer may be clinically beneficial. To better understand this, both preclinical and clinical evaluation of hormonal-based therapy and complex molecular alterations of escape mechanisms are needed. Future studies could also capture post-hormonal therapy molecular and biological status of potential escape mechanisms, such as estrogen receptor alpha (ESR1) gene mutations, assessed in both tissue and peripheral blood circulating tumor DNA. As patients with recurrent or metastatic endometrial cancer may survive on hormonal therapy for many years, long-term evaluation is needed for these patients.

Many patients may not be physically fit for standard second-line chemotherapy, targeted therapy with immunotherapy, clinical trials, or other regimens with potentially greater toxicity. The ability to offer tolerable therapeutic options to mismatch repair proficient endometrial cancer patients with chemotherapy-sparing regimens is crucial. The combination of onapristone and anastrozole may be a feasible approach for future pragmatic clinical trial designs, which would allow participation of elderly and frail patients with mismatch repair proficient recurrent or metastatic endometrial cancer.

5. Conclusions

The molecular and therapeutic landscape of recurrent or metastatic endometrial cancer is rapidly evolving with multiple promising developmental agents and biomarker-directed therapies. Oral onapristone and anastrozole could be used in combination as hormonal-targeted therapy and suggest an improvement in median progression-free survival over single-agent hormonal therapy. This chemotherapy-sparing option has the potential to provide durability in response with a high disease control rate with a favorable safety profile

for suitable patients. The OATH phase II study suggests potential therapeutic efficacy, safety, and tolerability utilizing onapristone and anastrozole in the treatment of patients with recurrent or metastatic hormone-receptor-positive, mismatch repair-proficient endometrial cancer.

AVAILABILITY OF DATA AND MATERIALS

Data available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

IM—acquired data and wrote the manuscript. MSS, MIE, NGR, SB, TB, ERB, AB, RJS—helped with writing the manuscript. TZ, AD—helped with statistical support. TS—helped with drafting the manuscript and final approval of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional review board of Thomas Jefferson University Hospital, #20P.829. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki; the International Council for Harmonisation Consolidated Guideline E6 for Good Clinical Practice; and applicable US, European, and Japanese regulatory requirements. All participants provided written informed consent.

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CONFLICT OF INTEREST

IM reports personal fees from OncLive. MS reports institutional grants from GSK, Merck, AZ; consulting fees from Merck, GSK, AZ, AbbVie, Caris, Eisai, Genmab, Myriad, Saxton, and Stump; advisory for Unite for Her. ME reports familial fees from Merck and Pfizer. NR reports no conflicts. AD reports no conflicts. SB reports personal fees from GatherED and OncLive. TZ reports no conflicts. TB reports no conflicts. TS reports that he was CMO of Context Therapeutics at the time of this study. EB reports no conflicts. AB reports no conflicts. RS reports fees from Incyte, advisory DSM Eisai, and Celsion.

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