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A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium

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SUMMARY

Objective. The aim of this study was to examine the tolerability and efficacy of combination bevacizumab rucaparib therapy in patients with recurrent cervical or endometrial cancer.

Patients & methods. Thirty-three patients with recurrent cervical or endometrial cancer were enrolled. Patients were required to have tumor progression after first line treatment for metastatic, or recurrent disease. Rucaparib was given at 600 mg BID twice daily for each 21-day cycle. Bevacizumab was given at 15 mg/kg on day 1 of each 21-day cycle. The primary endpoint was efficacy as determined by objective response rate or 6-month progression free survival.

Results. Of the 33 patients enrolled, 28 were evaluable. Patients with endometrial cancer had a response rate of 17% while patients with cervical cancer had a response rate of 14%. Median progression free survival was 3.8 months (95% C·I 2.5 to 5.7 months), and median overall survival was 10.1 months (95% C·I 7.0 to 15.1 months). Patients with *ARID1A* mutations displayed a better response rate (33%) and 6-month progression free survival (PFS6) rate (67%) than the entire study population. Observed toxicity was similar to that of previous studies with bevacizumab and rucaparib.

Conclusions. The combination of bevacizumab with rucaparib did not show significantly increased anti-tumor activity in all patients with recurrent cervical or endometrial cancer. However, patients with *ARID1A* mutations had a higher response rate and PFS6 suggesting this subgroup may benefit from the combination of bevacizumab and rucaparib. Further study is needed to confirm this observation. No new safety signals were seen.

1. Introduction

Treatment options for patients with recurrent cervical cancer and recurrent endometrial cancer remain limited. Even with optimal care, median overall survival is 17–24 months [1–4]. When this protocol was developed, no single standard of care (SOC) option was preferred for ≥2nd line treatment of recurrent cervical cancer or recurrent endometrial cancer. One treatment option under investigation was bevacizumab, which in a phase II trial as a single agent was found to be well tolerated and active in patients with recurrent cervical cancer. Approximately 24% patients survived progression free for at least 6 months, and 11% patients had a partial response [5]. In June 2018 pembrolizumab was approved by the FDA for recurrent cervical cancer after prior systemic chemotherapy, which marked the first approval of an immune checkpoint inhibitor to treat cervical cancer [6]. However, response rates are poor with only 14% of patients exhibiting a response in the Keynote-158 study (although many are durable responses), and this intervention is not curative; thus, better options are urgently needed [7].

Recently, recurrent endometrial cancer has 2 new FDA approvals: pembrolizumab for recurrent endometrial cancer with mismatch repair deficiency or microsatellite instability-high status (based on the tissue agnostic FDA approval granted in May 2017) and pembrolizumab/lenvatinib for recurrent endometrial cancer with mismatch repair deficiency (September 2019) [8,9]. While all of these new approvals are welcome additions to options for patients with recurrent cervical and endometrial cancer following disease progression through first line

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systemic chemotherapy, additional active regimens are urgently needed to prolong progression free survival (PFS) and overall survival (OS) which are unacceptably short in both disease settings.

The majority of cervical cancer is caused by human papilloma virus (HPV) infection. The HPV E6 and E7 proteins inhibit tumor suppressor genes *TP53* and *RB*, respectively. This leads to decreased DNA damage repair and traps cells in the G1/S phase of replication causing cervical cancer cells to be potentially susceptible to therapies targeting G1/S phase regulatory proteins like PARP1/2. Use of PARP inhibitors, like rucaparib, may sensitize cervical cancer cells to chemotherapy or other targeted therapies by augmenting tumor damage and inhibiting a myriad of DNA damage repair pathways [10].

PARP inhibitors have also demonstrated efficacy treating cancers with homologous recombination deficiency (HRD), particularly those associated with *BRCA* mutations [11]. This is promising as genetic alterations which impact homologous recombination occur in approximately 50% of high grade serous ovarian cancers [12]. PARP inhibitors also possess the benefit of being a generally well tolerated, orally administered therapy, making them a desirable treatment option for recurrent diseases. While only a small percentage of solid tumors, including recurrent cervical and endometrial cancer demonstrate HRD, around 24% of endometrial cancers and 20% of cervical cancers demonstrate a noticeable level of HRD [13,14]. One of the most commonly mutated genes in endometrial cancer is phosphatase and tensin homolog (*PTEN*) [15]. Loss of function of *PTEN* or AT-rich interactive domain-containing protein 1A (*ARID1A*), another commonly mutated gene, leads to decreased DNA damage repair capabilities similar to the *BRCA* driven HRD phenotype [16–18]. While the majority of endometrial tumors tested demonstrating an HRD phenotype appear to be non-endometrioid [19] in endometrial cancers, *PTEN* loss of function was frequently observed in all TCGA subgroups except copy number high, with an overall incidence of approximately 57% [20]. This is promising as characterization of endometrioid endometrial tumors by HRD score (using the Myriad HRD assay) demonstrated an association between an HRD score ≥ 4 and decreased survival but increased in vivo and in vitro cell line response to the PARP inhibitor olaparib [21].

In order to induce sensitivity to PARP inhibition, strategies are needed to induce HRD within tumors. One demonstrated mechanism of turning an HR proficient tumor into an HRD tumor is via induction of chronic hypoxia with anti-angiogenic agents such as bevacizumab. Induced chronic hypoxia causes translational downregulation of DNA repair, which may increase susceptibility to DNA damaging or synthetically lethal agents, like PARP inhibitors, in these hypoxic cells [22]. Based on this rationale and the known efficacy of single agent bevacizumab treatment in both recurrent cervical and endometrial cancer, we conducted a phase II trial assessing the efficacy of combination rucaparib and bevacizumab therapy in patients with recurrent cervical or endometrial cancer.

2. Patients and methods

2.1. Study design

This study (ClinicalTrials.gov identifier: NCT03476798) was a prospective, single arm, open label phase II clinical trial designed to evaluate the efficacy of rucaparib and bevacizumab in patients with recurrent cervical cancer and recurrent endometrial cancer conducted at three sites: Stephenson Cancer Center at The University of Oklahoma Health Sciences Center (lead site), University of Minnesota, and University of Virginia. The primary objective was to determine the efficacy as measured by objective response rate (ORR) or rate of patients who are progression free at 6 months (PFS6).

2.2. Patient selection

Eligibility criteria included patients at least 18 years of age with histologically-documented carcinoma of the cervix or endometrium. Patients were required to have tumor progression after at least one of systematic therapy for stage IVB, recurrent or persistent squamous cell or adenocarcinoma of the cervix, or adenocarcinoma of the endometrium, and an ECOG performance status of 0, 1, or 2. In addition, they were required to have measurable disease per RECIST version 1.1, adequate organ function, and have a life expectancy of at least 3 months. Biopsies were obtained prior to treatment initiation for assessment of baseline tumor biomarkers. Somatic mutational analysis was performed utilizing commercially available tests (Foundation Medicine Inc., Cambridge, MA) per standard medical practice. These results were correlated with demographic and response data. Written informed consent was obtained from all patients prior to commencing the protocol treatment. All participating institutions were required to have the treatment protocol reviewed by their institutional review board.

2.3. Treatment

Rucaparib was orally administered twice daily on every day of the 21-day cycle at 600 mg BID at approximately 12-h intervals. Treatment was halted and a dose reduction was considered or implemented if the following was observed: grade 3 or 4 hematologic toxicity, grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea) or any grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Bevacizumab was administered on day 1 of every 21-day cycle at 15 mg/kg as a 30-, 60- or 90-min infusion. Management of bevacizumab related toxicities followed institutional guidelines. In order to maintain concurrent administration, if rucaparib was held, bevacizumab was as well. Patients were treated until disease progression or toxicity was noted, unless the patient withdrew consent.

2.4. Dose modifications

Dose reduction for rucaparib was conducted on patients with Grade 3 ALT/AST levels that did not decline within 2 weeks. If levels continued to rise, treatment was interrupted until symptoms resolved to ≤ Grade 2. Treatment with rucaparib could continue if: ANC ≥ 1.0×109/L, platelet count ≥75×109/L, non-hematologic toxicities ≤ CTCAE Grade 1 severity or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient. In cases of dose reduction rucaparib treatment was reduced to either 500 mg BID, 400 mg BID or 300 mg BID.

2.5. Statistical analysis

A 2-stage study design based was utilized to determine if a sufficient number of patients were progression free at 6 months or had objective responses to treatment to continue the study into the second stage [23]. The null hypothesis is H_0: $\pi_r \leq 11\%$ and $\pi_s \leq 24\%$ and the alternative hypothesis is H_a: $\pi_r \geq 31\%$ ($=11\% + 20\%$) or $\pi_s \geq 44\%$ ($=24\% + 20\%$), where π_r is the ORR, π_s is the PFS6 rate, 11% and 24% are the ORR and PFS6, respectively. The 11% and 24% cutoffs were based on results from the bevacizumab trial by Monk et al. [5]. With 0.1 α level and at least 90% power, 28 eligible and evaluable patients were evaluated at the first stage with the intention that the study would continue to the second stage if either ≥5 patients had objective responses or ≥ 8 patients were progression free at 6 months.

Data were descriptively summarized using mean, SD, count and percentage. The ORR per RECIST guidelines (sum of complete responses and partial responses) was computed using 28 evaluable patients, and a 95% confidence interval (95% CI) was constructed based on the binomial distribution. Progression-free survival was defined as the time from registration until progression or death from any cause (whichever occurred first). OS was defined as the time from registration until death from any cause. Survival curves were estimated for all evaluable patients using the Kaplan–Meier method with 95% CI using the method described by Kalbfleisch and Prentice [24]. Confidence intervals for the

median survival times were obtained as described in Brookmeyer and Crowley [25]. SAS (version 9.4) was used for all analyses.

3. Results

Out of 33 recruited patients, 28 were evaluable for response (2 withdrew, 2 did not receive enough medication [at least 80% of all doses], and 1 died prior to first evaluation). Median age was 60.5 years (range, 30–74). Most patients were White (82.1%), 12.1% were Black, and 3.6% self-identified as Hispanic (Table 1). The majority of patients had endometrial cancer (81.8%; see Table 2). All patients had undergone at least one line of prior chemotherapy; most (66.7%) having received carboplatin/paclitaxel treatment. Adverse events led to permanent discontinuation in four patients (12%), eleven (33%) had a dose reduction/delay, and another eleven (33%) had treatment that was temporary interrupted. Grades of adverse events (AE) experienced are listed in Table 3. A table of AE by preferred term can be found in Supplemental Table S1.

Of the 28 evaluable patients, the median PFS was 3.8 months (95% CI 2.5, 5.7 Mo) (Fig. 1a). Median OS was 10.1 months (95% CI 7.0, 15.2 Mo) (Fig. 1b). The PFS6 for endometrial cancer was 30% (95% CI 0.1 to 0.5), and for cervical cancer it was 22% (95% CI 0.0 to 0.6). Among patients with primary endometrial cancer, the ORR was 14%, and those with cervical cancer had an ORR of 17%. Median follow up time was 25 months.

Eighteen total patients underwent FoundationOne tumor molecular profiling, 16 with endometrial cancer and 2 with cervical cancer. When evaluating molecular profiling results, *ARID1A* mutations were one of the most frequently observed genomic alterations (6/18, 33%). Patients with *ARID1A* mutations predominately had recurrent endometrial cancer (5/6 patients) while only 1 patient had recurrent cervical cancer (Table 4). A full list of identified genetic mutations by tumor site and type can be found in Supplemental Table S2. Patients with *ARID1A* mutations displayed a markedly higher response rate (33%) and PFS6 rate (66.7%) than that observed in the entire study population (10.7% and 21%, respectively). The proportion of patients meeting at least one of the primary endpoints was significantly higher in patients with *ARID1A* mutations versus those without, 83% vs 16% ($p = 0.0128$). Similarly, their PFS was longer at 8.8 months ($p = 0.019$) versus 2.6 months ($p = 0.0028$). *PTEN* mutations were found in 5 patients all with endometrial cancer (Table 4). ORR of patients with a *PTEN* mutation was 40% (2/5) compared to 15% (2/13) for subjects without *PTEN* mutations. The PFS6 rate for patients with *PTEN* mutations was 20% versus 46% for those without a *PTEN* mutation.

Grade 3 or 4 reported adverse events attributed to study treatment were rare with the most common being fatigue, nausea, and vomiting occurring in 1.3%, 1.1%, and 0.9% of patients, respectively. Similar toxicity was noted as previously reported with class-specific effects for each agent noted and no new safety signals were observed (Table 3 & Supplemental Table S1).

The study hypothesis was evaluated in a two-stage design, and the interim analysis occurred once 28 evaluable patients were enrolled per the study protocol. If ≥8 patients remained progression-free at six months or ≥ 5 objective responses were observed, then the study would move on to the second stage. Only 6 patients met the PFS6 bar and 4 had an objective response; 3 experienced a partial response and 1 experienced a complete response (Fig. 2), for an ORR of 18% (Fig. 1a). Thus, the study was terminated after the interim analysis.

Table 1
Distribution of patient characteristics ($n = 33$).

	Statistic	Total ($n = 33$)	
Age (years)		*n*	33
		Mean (SD)	60.42 (12.096)
		Median	64
		IQR[a]	16
		Min, Max	30, 74
BMI		*n*	32
		Mean (SD)	33.53 (8.786)
		Median	31.3
		IQR[a]	12.7
		Min, Max	17.87, 51.37
Race	American Indian		2 (6.1%)
	Black		4 (12.1%)
	White		27 (81.8%)
Ethnicity	Hispanic or Latino		1 (3%)
	Not Hispanic or Latino		32 (97%)
Primary Site	Cervix		6 (18.2%)
	Endometrium		27 (81.8%)
Cell Type	Cervix - Adenosquamous		3 (9.1%)
	Cervix - Carcinosarcoma		1 (3%)
	Cervix - Clear Cell Carcinoma		1 (3%)
	Cervix - Squamous Cell Carcinoma		1 (3%)
	Endometrial - Carcinosarcoma		3 (9.1%)
	Endometrial - Endometrioid		15 (45.5%)
	Endometrial - Mixed Carcinoma		2 (6.1%)
	Endometrial - Other		1 (3%)
	Endometrial - Serous Carcinoma		6 (18.2%)
History of Bevacizumab	No		23 (69.7%)
	Yes		10 (30.3%)

[a] IQR = Interquartile range.

Table 2
Pre-existing conditions (n = 33).

Pre-existing Condition		Total (n = 33)
Diabetes	No	25 (75.8%)
	Unknown	1 (3%)
	Yes - Type II	7 (21.2%)
Congestive Heart Failure	No	32 (97%)
	Yes	1 (3%)
Hypertension	No	19 (57.6%)
	Yes	14 (42.4%)
Peripheral Heart Disease	No	32 (97%)
	Yes	1 (3%)

4. Discussion

Patients with recurrent endometrial cancer or recurrent cervical cancer are a heterogeneous group likely requiring a diverse set of treatment options based on factors such as type of prior therapy, site of recurrence, histology, and tumor genetics/molecular class [26]. The disease rarity and scarcity of randomized prospective data on recurrent endometrial and cervical cancer has made determining optimal

Table 3
Treatment emergent adverse events by drug and CTCAE grade (n = 33).

	Overall		Related to Bevacizumab		Related to Rucaparib	
AE Grade	*n*	%	*n*	%	*n*	%
1	3	9.1	2	6.1	7	21.2
2	8	24.2	10	30.3	8	24.2
3	13	39.4	15	45.5	12	36.4
4	6	18.2	2	6.1	3	9.1
5	3	9.1	0	0.0	0	0
None	0	0.0	4	12.1	3	9.1
Total	33	100	33	100	33	100

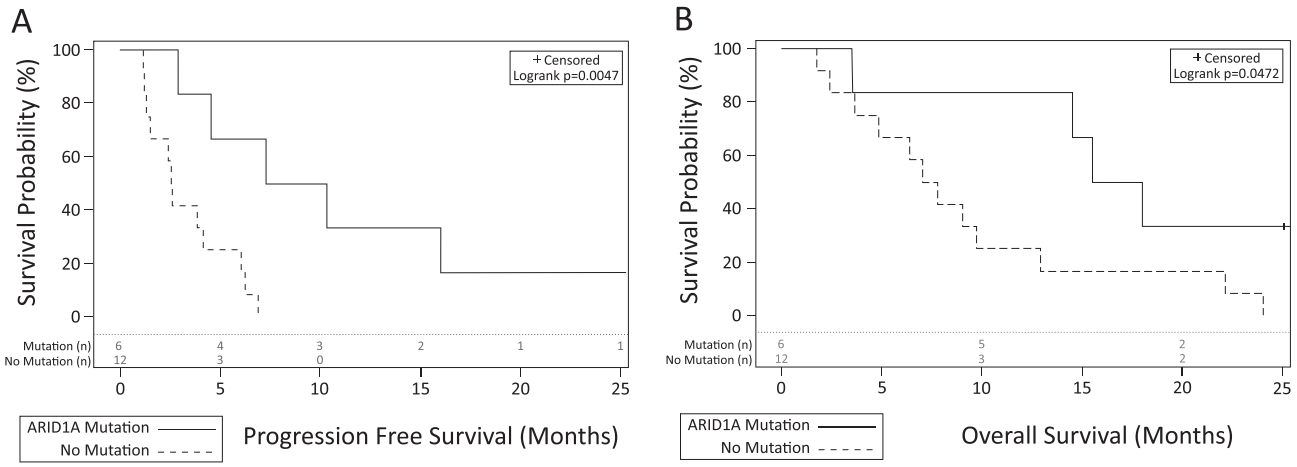

Fig. 1. Cumulative A) Progression free survival and B) overall survival rates, by ARID1A status ($n = 28$). PFS and OS rates for the entire population fall in-between the two KM curves.

treatments of these diseases difficult, as evidenced by the poor survival durations noted upon disease recurrence or persistence.

This trial was initiated to examine the efficacy of combination rucaparib and bevacizumab treatment. Bevacizumab administered as a single agent has been shown to be an effective therapy with 11% and 14% response rates and 24% and 40% PFS6 rates in recurrent cervical cancer and recurrent endometrial cancer, respectively [5,27]. Prior pre-clinical studies have indicated a potential synergistic effect with the addition of rucaparib to bevacizumab [28–31]. This is due to the fact that use of anti-angiogenic agents such as bevacizumab induce cellular hypoxia. In the setting of cellular hypoxia, HRD is induced by downregulation of homologous recombination repair genes such as *RAD51* and *BRCA1* leading to presumed enhanced susceptibility to PARP inhibition [32].

This drug combination was well tolerated by the study population. Unfortunately, the expected clinical benefit was not observed in the overall group of patients enrolled in this trial. However, the ORR of 17% in cervical cancer patients is similar but actually somewhat higher than that observed in Keynote-158 (14%), which led to the FDA indication for monotherapy in recurrent cervical cancer patients. It is not clear why this regimen had numerically slightly greater efficacy, but cross-trial comparisons are fraught with error.

When evaluating molecular profiling results, *ARID1A* mutations were one of the most frequently observed genomic alterations (6/18, 33%). Most of the patients with *ARID1A* mutations had recurrent endometrial cancer, and displayed a markedly higher response rate (33%) and PFS6 rate (67%) than that observed in the entire study population (10.7% and 21% respectively). Additionally, a significantly higher proportion of patients with *ARID1A* mutations met at least one primary endpoint of the study suggesting there may be benefit to treating this subpopulation of patients with combination rucaparib and bevacizumab therapy.

The finding of greater efficacy in our relatively small group of patients with *ARID1A* mutations is consistent with prior literature correlating *ARID1A* mutations with increased sensitivity of cancer cells to PARP inhibitors [33]. *ARID1A* is a subunit of highly conserved SWI/SNF chromatin remodeling complex responsible for repositioning nucleosomes to modulate DNA accessibility to cellular processes involved in chromatin structure. It functions as a tumor suppressor gene by interacting with ATR at sites of double stranded DNA breaks. If *ARID1A* function is lost, it leads to impaired G2/M checkpoint activation and renders cells sensitive to double stranded break-inducing therapies, i.e. PARP inhibitors [34–36]. Cancers with *ARID1A* mutations also have increased sensitivity to anti-angiogenic therapy [34]. *ARID1A* deficient hepatocellular carcinoma has been shown to have higher vessel density and enhanced angiogenesis by virtue of ectopic Ang2 production, leading to profound sensitivity to Ang2 specific inhibitors such as sorafenib [37]. *ARID1A* loss may regulate other oncogenic pathways such as increased PD-L1, PIK-3CA activating mutations, or DNA methylation [36]. Overexpression of VEGF, which is commonly observed in endometrial and cervical cancers, may lend to further sensitivity to bevacizumab and other anti-angiogenic therapies.

Table 4
ARID1A and PTEN status by tumor location and type (n = 18).

	Histology	*ARID1A*	*PTEN*	No Mutation
Cervical ($n = 2$)	Adenosquamous	0	0	0
	Carcinosarcoma	0	0	1
	Clear Cell Carcinoma	0	0	0
	Squamous Cell Carcinoma	1	0	0
	Total	**1**	**0**	**1**
Endometrial ($n = 16$)	Carcinosarcoma	0	0	2
	Endometrioid	3	3	4
	Mixed Carcinoma	1	2	0
	Serous Carcinoma	1	0	2
	Other	0	0	1
	Total	**5***	**5***	**9**

* Three patients experienced both *ARID1A* and *PTEN* mutations.

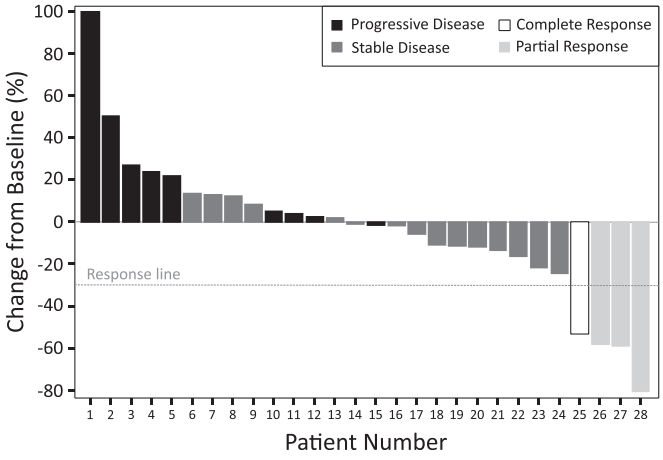

Fig. 2. A waterfall plot of best response to combination bevacizumab rucaparib therapy. The change from baseline was assessed according to RECIST version 1.1 with a 30% reduction denoting at least a partial response ($n = 28$).

While we noted 7 different types of *ARID1A* mutations, the heterogeneity of mutational type and variety of histologic subgroups limits conclusions that may be drawn from this small study. However, there are similar ongoing studies examining use of PARP inhibitors in recurrent endometrial cancers that include *ARID1A* status such as NCT03586661 at the MD Anderson Cancer Center. As further characterization of the impacts of *ARID1A* mutations on clinical response and outcome is critical, we currently have a phase 2 trial with integral biomarkers planned.

There are several notable limitations of this study including its single-arm design, relatively small sample size, limited use of molecular profiling, heterogeneity of tumor types/locations, and homogeneity of patients enrolled. This last concern is especially troubling. Despite the liberal inclusion criteria of this trial, there was still a significant lag in equitable accrual of Black women who are disproportionately impacted by cervical and endometrial cancer. This is a continuation of a disturbing historical trend rooted in colonization and systemic racism both within and outside of the medical system [38–43]. Factors that contribute to this lag such as lack of access to healthcare, health insurance, financial means, transportation, childcare, and education [44,45] are driven largely by the results of historical racism acting in combination with current policy choices that reinforce social and systemic racism through economic and institutional means [42,46–48]. Subsequently, many of these factors fall outside the immediate influence of clinicians and likely require large policy shifts geared towards equitable economic redistribution, like implementation of universal healthcare and childcare, to address. However, factors such as providing high-quality transportation, regular community engagement, prioritizing recruitment of Black women in the overall recruitment strategy, increasing Black physician and staff involvement in clinical trials (especially recruitment), prioritizing informing and educating Black patients about clinical trials, and providing culturally-appropriate and sensitive care are things clinics can and should do to combat this disparity [44].

In summary, rucaparib/bevacizumab therapy was not found to be an active regimen in unselected patients with recurrent endometrial and cervical cancer despite being well tolerated. However, a subset of patients may reap benefit based on their molecular characterization. Further evaluation is needed to confirm and characterize this benefit.

Author contributions

Dr. Gunderson contributed to trial design and execution, patient enrollment, data analysis, and manuscript preparation.

Dr. Moore contributed to trial design, patient enrollment, data analysis, and manuscript preparation.

Drs. Cantrell, Erickson, Duska, Richardson, Landrum, Holman, Walker, and Moxley contributed to patient enrollment and provided data for study.

Dr. Queimado contributed to development and execution of translational studies, data analysis, and manuscript preparation.

Dr. Cohoon and Ding contributed to statistical design and analysis of data and manuscript preparation.

Dr. Dockery contributed to trial design and protocol development, data analysis, and manuscript preparation.

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Author disclosures

KNM serves on advisory boards for Alkemers, Aravive, Astra Zeneca, Blueprint pharma, Eisai, EMD/Serono, GSK/Tesaro, Genentech/Roche, Hengrui, Immunogen, IMab, INXMED, Jazz, Lilly, Merck, Mereo, Mersana, Myriad, OncXerna, OncoNova, EQRX, Tarveda, and VBL Therapeutics. They have received research funding from PTC Therapeutics, Lilly, Merck, and GSK/Tesaro. They also serve as an Associate Director for GOG Partners, NRG Ovarian Cancer Chair and GOG Foundation Board of Directors. **DLR** serves on advisory boards for AstraZeneca, Genentech, Mersana, and GlaxoSmithKline. **LRD** reports personal fees from Astra Zeneca, grants, personal fees and other from Genentech/Roche, grants from Cerulean/NextGen/(GOG 3008), grants from AbbVie/(GOG 3005), grants from Tesaro, grants from Pfizer, grants and other from GlaxoSmithKlein/Novartis, grants from Morab, grants and personal fees from MorphoTek, grants, personal fees and other from Merck, grants from Aduro BioTech, grants from Syndax, grants from Ludwig, grants from LEAP Therapeutics, grants from Eisai, grants from Lycera, grants and personal fees from Genentech/Roche, grants and personal fees from Inovio, personal fees from Advance Medical, personal fees from UpToDate, personal fees from Cue Biopharma, personal fees from British Journal of OB/GYN, personal fees from Parexel, personal fees from State of California, personal fees from Elsevier, personal fees from ASCO, personal fees from Expert review, personal fees from ClearView Health Care, personal fees from National Cancer Institute, personal fees from JB Learning, grants from Advaxis, outside the submitted work.

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