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Phase II study of enzalutamide in androgen receptor positive, recurrent, high- and low-grade serous ovarian cancer

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CONFLICTS OF INTEREST

None declared

DISCLOSURES

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Abstract

Objectives: We sought to determine the safety and efficacy of the oral androgen receptor antagonist enzalutamide in patients with previously treated, recurrent, AR-positive (AR+) ovarian cancer.

Methods: This was a single-institution phase II study of patients with AR+ ovarian cancer with measurable disease with 1–3 prior lines of chemotherapy; patients were screened for enrollment from 11/2013–7/2018. Following consent, archival tissue was evaluated for AR+. Enrolled patients received daily enzalutamide 160 mg until progression of disease or treatment discontinuation. Adverse events were graded by CTCAE v4.0. Co-primary endpoints were 6-month progression-free survival (PFS_6) and overall response rate (ORR) by RECIST 1.1 criteria.

Results: During the study period, 160 patients were screened and 59 (45 high-grade serous [HGS] and 14 low-grade serous [LGS]) consented to treatment on study. There was 1 confirmed and 1 unconfirmed partial response. The ORR was 1.7% (90% CI: 0.2–100%). The overall PFS_6 rate (as binary) was 22% (90% CI: 15.1–100%). The 6-month PFS rate (as time to event) was 19.8% for HGS patients (90% CI: 12.7–100%) and 38.5% (90% CI: 21.7%−100%) for LGS patients. Grade 3 toxicities occurred in 6 patients (one toxicity (Grade 3 rash) was considered a dose-limiting toxicity). One patient died of cardiac arrest after 42 days on treatment of a cardiac arrest not attributed to study drug.

Conclusions: The study met its primary endpoint, with a PFS_6 rate of 22% (n=13); however, the overall response rate was low. Enzalutamide was well tolerated and may be a potential treatment option in select patients.

Keywords

Ovarian cancer; Serous ovarian cancer; Recurrent ovarian cancer; Enzalutamide; Androgen receptor expression

INTRODUCTION

Epithelial carcinoma of the ovary accounts for approximately 90% of ovarian, tubal, and peritoneal cancers, and up to 80% of advanced-stage patients ultimately recur (1, 2). Despite high rates of recurrence, 25–32% of patients with advanced-stage disease will survive 10 years or longer (3, 4). With each recurrence, however, treatment strategies shift, and patients can require multiple lines of therapy as chemoresistance progresses. Therefore, the identification of active targeted agents with good tolerability is important.

Forty-four percent to 90% of epithelial ovarian carcinomas are androgen receptor positive (AR+), representing a potential targetable pathway (5–8). Preclinical data have demonstrated

that AR+ ovarian cancer cells show increased cell division when exposed to androgens and that this activity is reversed with androgen inhibition (9). It has been hypothesized that AR+ ovarian tumors may preferentially respond to AR antagonists. A prior phase II study by our group investigated the efficacy of dual anti-androgen and gonadotropin-releasing hormone analog therapy with bicalutamide and goserelin in patients with epithelial ovarian cancer, and found no survival benefit (10). Of note, the study was performed with a less potent, first-generation AR antagonist in an unselected patient population, of whom only 58% were AR+ (11).

Enzalutamide is an orally available, potent, and selective small-molecule second-generation AR antagonist that slows growth and induces cell death in AR-expressing tumor cells. Unlike first-generation AR antagonists such as bicalutamide, enzalutamide works through three mechanisms: by blocking testosterone binding, impeding nuclear translocation of the AR, and inhibiting binding of the AR to DNA in the nucleus (11). Preclinical data have demonstrated that enzalutamide is superior to bicalutamide in both cell line and mouse xenograft models, and it has demonstrated efficacy for androgen blockade in prostate cancer (11, 12). The drug also has a compelling safety and tolerability profile, with only 2–5% of patients in large clinical trials discontinuing enzalutamide secondary to adverse events (13, 14). We sought to determine the safety and efficacy of enzalutamide in patients with previously treated, recurrent, AR+ ovarian cancer.

METHODS

This single-institution, phase II study with safety lead-in was designed to evaluate the activity and safety of enzalutamide 160 mg oral daily treatment in patients with recurrent AR+ epithelial ovarian cancer, with measurable disease, who had undergone 1–3 prior lines of chemotherapy. The primary endpoints were to estimate the proportion of women surviving progression-free for at least 6 months (PFS_6) and the proportion of patients who experienced an objective tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Secondary endpoints included determining the frequency and severity of adverse events in patients treated with enzalutamide, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. The study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board, and all patients enrolled in the study provided written informed consent to participate.

Patients

Patients were eligible for enrollment if they were ≥18 years of age, had a histologically confirmed diagnosis of AR+ epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, and had undergone 1–3 prior lines of cytotoxic treatment, including ≥1 platinum-based chemotherapy. Eligible patients had measurable recurrent or persistent disease (as defined by RECIST 1.1 criteria) that had progressed (defined as radiologic and/or clinical progression) on or after last therapy and was not amenable to surgery with potentially curative intent. Patients were required to have a Karnofsky Performance Status (KPS) score of ≥70%. Patients were excluded if they had a condition precluding adequate study drug

absorption or were unable to tolerate oral medications, had prior use of an AR antagonist or androgen synthesis inhibitor or had participated in a clinical trial evaluating such agents, had known brain metastases or a history of seizure, had a history of uncontrolled hypertension or clinically significant heart disease, or had persistence of Grade 2 or higher toxic effects of prior therapy by NCI CTCAE version 4.0 (excluding Grade 2 neuropathy or Grade 2 alopecia, which were allowed). For a description of full study eligibility criteria, please see supplemental data.

Screening for AR positivity was performed from archival formalin-fixed paraffin-embedded tumor tissue in a CLIA (Clinical Laboratory Improvement Amendments)-approved laboratory with immunohistochemistry (IHC) using the Ventana androgen antibody (Roche); AR expression ≥5% was required for study entry (Figures 1 and 2). If no archival tissue was available, patients were required to undergo a tumor biopsy for study enrollment consideration. In cases where multiple samples were available, 3 IHCs were performed. If the patient had ≥1 slide with ≥5% AR tumor staining, she was considered eligible for enrollment.

Study design

This was a single-arm, open-label, phase II, single-institution study. All patients were enrolled and treated at Memorial Sloan Kettering Cancer Center. To reduce patient risk, a safety lead-in phase was designed and included 15 patients. By applying Bayesian methodology from Gonen et al, a detailed probability table of dose-limiting toxicity (DLT) was provided (details in the protocol; see supplemental data) (15). The probability of a DLT exceeding 0.3 was 66% with 5 DLTs in the safety lead-in cohort. This was chosen as the most appropriate threshold for putting the trial on hold.

After the safety lead-in phase, a two-stage, phase II trial was designed to evaluate the efficacy of enzalutamide by employing a previously reported method by Sill and Yothers (16). PFS_6 and overall response rate (ORR) were the co-primary endpoints. We hypothesized that treatment with enzalutamide would result in a PFS_6 rate increase from 15% to 30% or an ORR increase from 5% to 20%. The treatment would be considered of clinical interest and worthy of further investigation if either endpoint was met. The first stage would accrue 28 eligible patients. The second stage, which would enroll an additional 31 patients, would open if ≥3 patients experienced a clinical response and/or ≥5 patients did not progress/die at 6 months. The study would be considered positive if there were ≥7 clinical responses and/or ≥13 progression-free survivors among 59 patients. The power of the design was ≥0.9 (ORR and PFS_6) with a type 1 error range 0.09–0.1 (detail in the protocol; see supplemental data). The patients in the safety lead-in phase would be included in the first stage.

Patients who died from any cause or were lost to follow-up (including patients who discontinued treatment due to toxicity, or who withdrew consent) within 6 months were considered failures for the PFS_6 binary outcome. ORR and PFS_6 were reported assuming binomial proportions, with exact binomial confidence intervals (CIs). Overall response was defined by RECIST 1.1 criteria. PFS was also analyzed with time-to-event methodology using treatment start date as time zero, and progression was identified by clinical

progression as well as progression of disease according to RECIST 1.1 criteria. Median PFS and PFS rate were summarized using the Kaplan-Meier method. Reported CIs were one-sided 90% CIs. The association of AR expression (on a scale of 0–100%) with ORR and PFS was determined using the two-samples Wilcoxon test (for ORR) and Cox Proportional Hazards model (for PFS).

Study treatment

After determination of eligibility, patients received 160 mg (4 capsules) of enzalutamide by mouth daily and continued with study drug until progression of disease, unacceptable toxicity, or withdrawal from the study. Tumors were assessed every 8 weeks (±1 week) while on treatment, as well as at the end of the study with computed tomography (CT) or magnetic resonance imaging (MRI).

Toxicity assessment

Toxicities were evaluated during physician assessments performed every 2 weeks during the first cycle (28 days) and, thereafter, every 4 weeks during subsequent treatment cycles; toxicities were graded using CTCAE version 4.0 criteria. DLTs were defined as any event consistent with a seizure of any grade, grade ≥3 diarrhea, nausea, or vomiting that did not improve to grade 1 within 14 days of initiating standard of care therapy, grade ≥3 decreased platelet count with associated bleeding, grade ≥3 absolute neutrophil count (ANC) that persisted for 7 or more days or that was associated with fevers (febrile neutropenia), any other grade ≥3 non-hematologic toxicity determined to be related to the study drug. Grade 1 or 2 toxicities were treated with supportive care. Grade ≥3 toxicities considered related to enzalutamide prompted cessation of enzalutamide until the toxicity resolved to grade ≤1. Report of DLTs resulted in the option to withdraw from study or continue study treatment following adequate recovery and dose modification.

RESULTS

Patient characteristics

One hundred sixty-five patients were screened for enrollment between November 2013 and July 2018. Of these 165 patients, 145 had sufficient tissue to test for AR positivity, 87 (60%) were deemed AR+, and 59 consented to treatment.

Baseline demographics and disease characteristics of the study population are presented in Table 1. Median patient age was 64 years (range, 29–87 years). Median body mass index (BMI) was 26 kg/m^2 (range, 19.8–56.4 kg/m^2). Forty-five patients (76.3%) had high-grade serous (HGS) carcinoma and 14 (23.7%) had low-grade serous (LGS) carcinoma. Most patients had received 2 (54.2%) or 3 (27.1%) prior lines of chemotherapy.

Primary endpoints and efficacy

The results presented here include an assessment of endpoints (PFS_6, ORR) up to the data cut-off date of July 30, 2019. At the time of data cut-off, all patients had discontinued enzalutamide. The most common reasons for discontinuing treatment were disease progression by RECIST (n=50), clinical progression (n=3), adverse events (n=4),

withdrawal of consent (n=1), and death (n=1). The median duration of exposure to enzalutamide was 2.1 months (range, 0.4–32.3 months).

After enrollment of the first 28 patients, 7 patients remained progression-free for 6 months, which met criteria for expanding the trial to its second stage for a total enrollment of 59 patients. Among this total cohort, 13 of 59 patients (22.0%; 90% CI: 15.1–100.0%) remained progression-free for ≥6 months. Among the 13 patients with PFS ≥6 months, 5 had 3 prior lines of chemotherapy, 7 had 2 prior lines of chemotherapy, and 1 had 1 prior line of chemotherapy. For the secondary endpoint, considering PFS as time to event outcome, the median PFS was 1.7 months for HGS and 4.6 months for LGS. The PFS rate at 6 months for HGS patients was 19.8% (90%CI: 12.7–100%) and for LGS patients 38.5% (90%CI: 21.7–100%) (Figure 3).

Of 59 patients, 1 patient with HGS had a confirmed response by RECIST 1.1, for an ORR of 1.7% (90% CI: 0.2–100%). One other LGS patient had an unconfirmed response, with a partial response by RECIST demonstrated on her initial imaging, followed by clinical progression prior to her second radiographic tumor assessment.

AR positivity and response

Among the study population, median AR expression was 60% (range, 5–99%). There was no significant association between AR expression and PFS (HR, 0.98; 95% CI: 0.92-NR; p=0.674). For the 13 patients with PFS ≥ 6 months the mean level of AR expression was 56% and the median level of AR expression was 70% (range 5–99%). The patient who experienced a partial response by RECIST had 10% AR expression; the patient who experienced an unconfirmed response had 40% AR expression. Level of AR expression by quartile was also examined and median PFS and percentage of patients progression free at 6 months for each quartile reported in Table 2; no difference was found between quartile defined categories by logrank test (p=0.81).

Safety

Grade 3 adverse events were reported in 17 (29%) patients. Events non-attributable to the study drug included 9 episodes of electrolyte disturbances, 7 episodes of lymphopenia, 4 episodes of anemia, 2 episodes of thrombocytopenia, 1 episode of abdominal pain, 1 small bowel obstruction, 1 abdominal infection, 1 colitis, 1 rash, 1 thromboembolic event, 1 episode of hypertension, 1 hip fracture, 1 episode of hearing impairment, and 1 episode of Grade 3 weight loss. In total, 6 (10%) patients experienced Grade 3 toxicities attributed to the study drug, including 2 (3%) with rash, 1 (2%) with fatigue, 1 (2%) with new-onset hypertension, 1 (2%) with anemia, and 1(2%) with transaminase elevation. One of these Grade 3 toxicities, a Grade 3 rash with onset 10–12 days after initiation of enzalutamide, was classified as a dose-limiting toxicity (DLT) that led to study discontinuation. In addition, 2 (3%) patients experienced Grade 4 events non-attributable to the study drug (episodes of neutropenia). One patient died due to a cardiac arrest (Grade 5 event); this was felt to be unrelated to study treatment and occurred after 42 days on treatment. The cardiac arrest occurred before her first scan and the patient was replaced; she was included in PFS_6 and ORR analysis.

DISCUSSION

For long-term survivors of epithelial ovarian cancer, many of whom experience multiple recurrences, it is important to have several well-tolerated treatment options that can be leveraged throughout a disease course. This phase II trial investigated the efficacy of enzalutamide, a well-tolerated oral AR antagonist, in recurrent AR+ epithelial ovarian cancer. This study met its primary endpoint, as PFS_6 was observed in at least 13 (22%) of 59 patients. More specifically, 19.8% of patients with HGS and 38.5% of patients with LGS met the PFS_6 endpoint. Furthermore, enzalutamide was well tolerated in this population; no patients reported a treatment-related grade >3 toxicity and only 6 (10.2%) reported a treatment-associated Grade 3 toxicity. Based on these findings, enzalutamide may be an option that can confer modest PFS benefits, with minimal toxicity, for selected patients with recurrent ovarian cancer.

Enzalutamide has proven to effectively suppress tumor growth in multiple disease sites that also have AR+ phenotypes, such as prostate cancer. In prostate cancer, the AFFIRM randomized, double-blind, placebo-controlled, phase III trial demonstrated a median overall survival (OS) difference of 4.8 months in men with metastatic castration-resistant prostate cancer treated with enzalutamide (13). Subsequently, the PROSPER randomized, double-blind, placebo controlled, phase III trial demonstrated a median OS difference of 10.7 months in men with non-metastatic castration-resistant prostate cancer treated with enzalutamide (21). These trials, among others, led to the FDA approval of enzalutamide in the treatment of castration-resistant prostate cancer (22). In endometrioid endometrial cancer, another AR+ phenotype, emerging data have demonstrated promising efficacy of enzalutamide in combination with chemotherapy. The phase II ENPAC trial investigated ORR and PFS_6 in 35 patients with advanced-stage or recurrent endometrioid endometrial cancer (23). Findings demonstrated the safety and promising efficacy of enzalutamide in this setting, with a 71% ORR (95% CI: 54%−85%) and 83% PFS_6 rate (95% CI: 66%−92%).

In ovarian cancer, initial trials of AR blockade have reported limited benefit of AR-targeted therapies. Levine et al. investigated dual hormonal blockade with bicalutamide (an oral nonsteroidal anti-androgen) and goserelin (a subcutaneous gonadotropin-releasing hormone analogue), and found that this combination conferred no significant PFS benefit in patients in second or higher remission (10). Similarly, studies on gonadotropin agonists such as letrozole have reported low ORRs (0–15%) and modest clinical benefit rates (up to 26%) in recurrent ovarian cancer (24–26). A phase II trial of anastrozole in platinum-resistant ovarian cancer reported an ORR of 0% and a clinical benefit rate of 27% (27). Studies on flutamide, a non-steroidal drug with anti-androgen properties, failed to demonstrate efficacy in patients with recurrent ovarian cancer (28, 29). More recently, a phase II trial reported the efficacy of abiraterone acetate, a CYP17 inhibitor that targets androgen synthesis, in patients with recurrent epithelial ovarian cancer. This study reported an ORR of 2.4% at 12 weeks, a clinical benefit rate of 26.2% at 12 weeks, and a PFS_6 rate of 16.7% (30). Of note, 27.5% of patients on this study had AR-negative disease. and greater than 20% had received 4 or more prior lines of treatment. Our study differed from these trials in three important ways: 1) patients were limited to 3 or fewer prior cytotoxic treatments; 2) all patients had confirmed

AR+ disease; 3) we used a second-generation AR antagonist, with greater potency than other agents such as bicalutamide.

Despite these parameters, only 1 of our patients experienced a confirmed partial response (ORR, 1.7%; 90% one-sided CI: 0.2–100%). There are several possible explanations for this low ORR. First, it is possible that targeting the AR pathway may suppress tumor growth but not actively decrease tumor burden. It is also conceivable that tumors readily circumvent the AR signaling pathway, which could potentially explain why there was no observed association between AR expression and PFS. This finding echoes that of other studies on AR blockade in ovarian cancer, which have also demonstrated no correlation between AR expression and outcomes with AR-targeted therapies (10). For example, Banerjee et al. reported no correlation between AR positivity and percent change in sum of target lesions or percent change in CA-125 in patients treated with the AR antagonist abiraterone (30). It is also possible that mechanisms of enzalutamide resistance, such as activation of mutated ARs, may have contributed to the low ORR, as has been demonstrated in patients with prostate cancer treated with abiraterone (31). Future studies may investigate whether dual hormonal blockade improves response rates to enzalutamide, as has been described in breast cancer studies (32).

There are several limitations to this study. Patients with AR+ archival tissue samples were permitted to enroll on trial. It is possible that AR expression had decreased with treatment cycles, and thus, archival tissue may not have been representative of the patient's current tumor biology (9). Furthermore, although we noted a higher PFS_6 rate (38.5%) in patients with LGS cancer, the sample size (n=14) was small, precluding a subset analysis of these patients. It is possible that subsequent investigation of enzalutamide may be most beneficial in low-grade histologies, as these patients can have prolonged disease courses requiring multiple lines of treatment, as well as broad chemoresistance.

In summary, our findings suggest a potential role for enzalutamide, particularly in the AR+ LGS subpopulation. In this scenario, it would be clinically beneficial to have another well-tolerated oral treatment option that can be used in recurrent disease. Further study of enzalutamide, perhaps in combination with other hormonal agents, may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Enzalutamide was well-tolerated in AR+ recurrent ovarian cancer patients and demonstrated a suitable safety profile.
- This study met its primary endpoint, as enzalutamide afforded modest progression-free survival.
- The overall response rate to enzalutamide was low, with less than 2% of patients demonstrating radiographic response.
- Further study of enzalutamide may be warranted, particularly in patients with AR+ low-grade serous ovarian cancer.

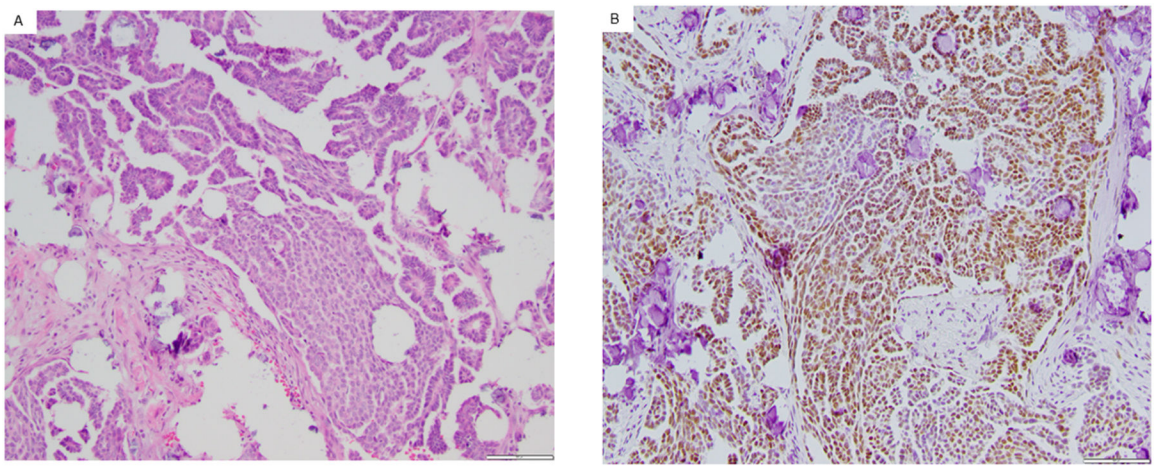

Figure 1:

Representative example of an Androgen Receptor positive low-grade serous ovarian carcinoma. Androgen Receptor (AR) expression was assessed in archival (fresh frozen paraffin embedded) or fresh tissue. Pictured is the hematoxylin and eosin stain of a low-grade serous carcinoma (A) as well as AR+ immunohistochemistry (B). Both images obtained with magnification of 100x.

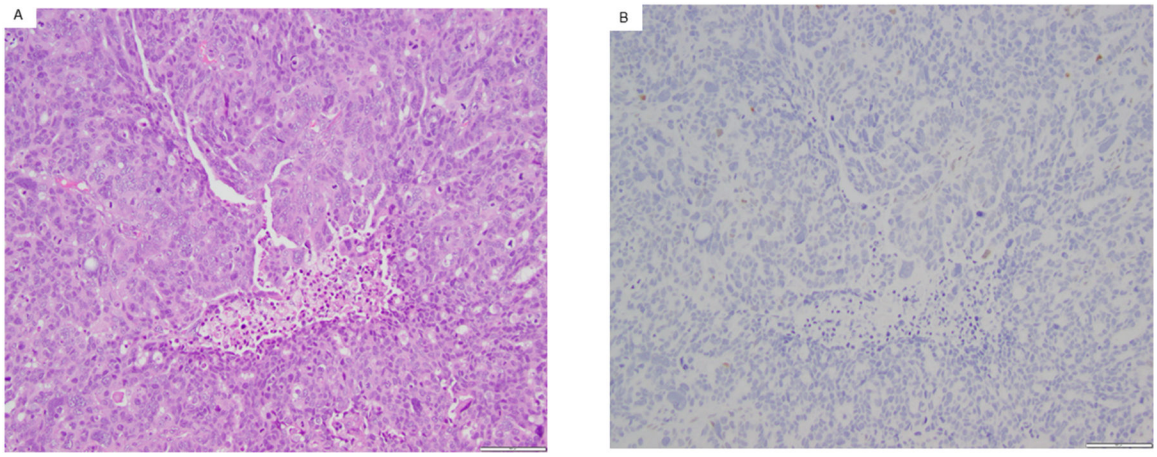

Figure 2:

Representative example of an Androgen Receptor negative high-grade serous ovarian carcinoma. Androgen Receptor (AR) expression was assessed in archival (fresh frozen paraffin embedded) or fresh tissue. Pictured is the hematoxylin and eosin stain of a high-grade serous carcinoma (A) as well as AR-immunohistochemistry (B). Both images obtained with magnification of 100x.

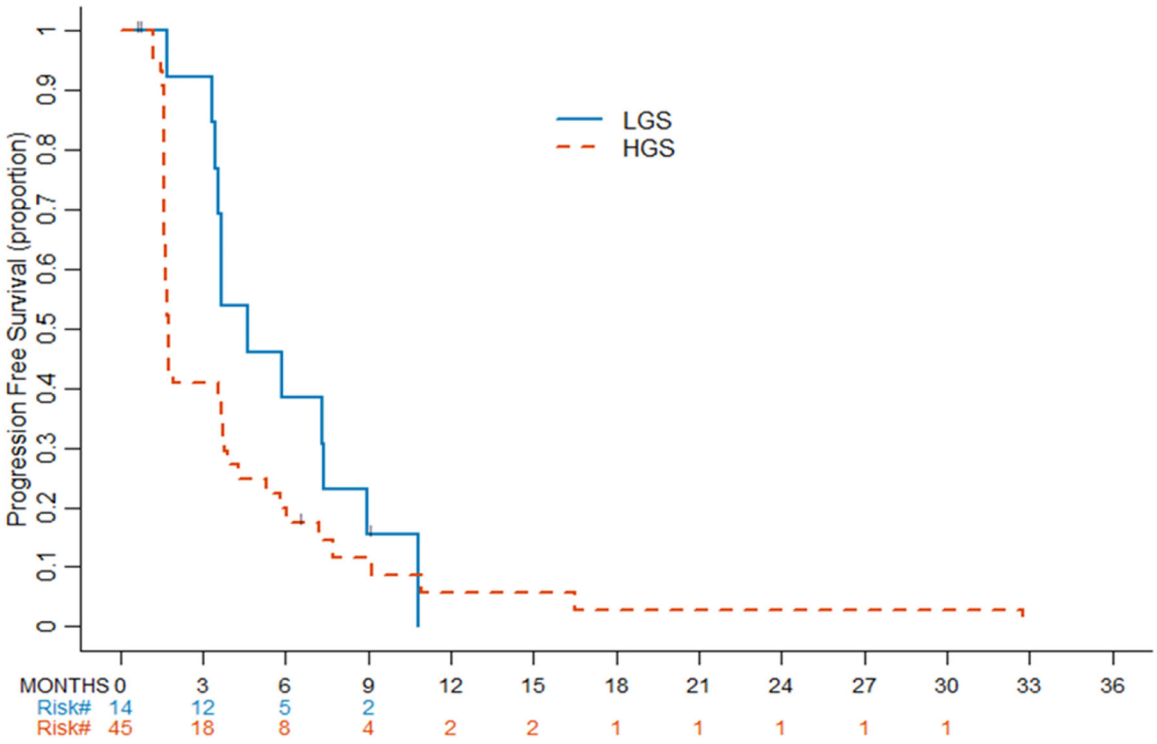

Figure 3:

Progression-free survival by histology. Kaplan-Meier curves for progression-free survival by histology. LGS, low-grade serous. HGS, high-grade serous.

Table 1:

Study population

Characteristic	N (%)
Race	
White	48 (81%)
Asian	5 (9%)
Black or African American	2 (3%)
Unknown	4 (7%)
Histology	
High-grade serous	45 (76%)
Low-grade serous	14 (24%)
Debulking surgery	
Optimal	53 (90%)
Suboptimal	5 (8%)
Unknown	1 (2%)
Prior lines of chemotherapy	
1 line	11 (19%)
2 lines	32 (54%)
3 lines	16 (27%)
Prior hormonal therapy	
No	46 (78%)
Yes	13 (22%)
Prior radiation therapy	
No	58 (98%)
Yes	1 (2%)

Table 2:

Median PFS and percentage of patients progression free at 6 months by quartile of AR expression.

% AR Expression	N	Progression/Death	Median PFS (90%CI)	PFS_6 (90%CI)	Logrank P value
<25%	14	12	1.7 (1.6-Inf)	23.1% (5.6–100%)	0.81
25–60%	15	14	1.9 (1.6-Inf)	13.3% (2.2–100%)	
60–80%	13	11	3.5 (1.6-Inf)	33.3% (10.3–100%)	
>=80%	17	17	3.7 (1.6-Inf)	29.4% (10.7–100%)	