Evolving treatment paradigms in metastatic or recurrent low-grade endometrial cancer: When is hormonal-based therapy the preferred option?

Haider Mahdi,[1,2] Isabelle Ray-Coquard ,[3] Domenica Lorusso,[4,5] Mansoor Raza Mirza,[6] Bradley J Monk ,[7] Brian Slomovitz [8]

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For numbered affiliations see end of article.

Correspondence to
Dr Brian Slomovitz, Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach FL 33140, Florida, USA; bslomovitz@gog.org

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ABSTRACT

Endometrial cancer is the most common gynecologic malignancy in developed countries, with increasing incidence and mortality rates worldwide. While most cases are successfully treated with surgery, first-line treatment options for metastatic or recurrent endometrial cancer involve significant toxicities. Imprecise classification of heterogeneous subgroups further complicates treatment decisions and interpretation of clinical trial results. Recent advances in molecular classification are guiding treatment decisions for metastatic or recurrent endometrial cancers. Integrating molecular characteristics with traditional clinicopathology can both reduce overtreatment or undertreatment and help guide the appropriate choice of therapies and effective design of future studies. Here we discuss the treatment of metastatic or recurrent low-grade endometrioid adenocarcinoma of the uterine corpus, which is distinct from high-grade tumors histologically, molecularly, and in treatment response.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in developed countries, ranking seventh among all cancers in women.[1 2] The estimated number of endometrial carcinoma cases in Europe was over 121,000, with over 29,000 deaths in 2018.[3] It is estimated that there will be over 66,000 new cases and over 13,000 deaths in the United States alone in 2023.[4]

Endometrial cancer is currently the only gynecological malignancy with increasing rates of incidence. Increased levels of estrogen, often caused by obesity or diabetes, is a significant risk factor for this disease.[1 4–6] Other risk factors include early age at menarche, nulliparity, late age at menopause, Lynch Syndrome, older age, unopposed estrogen, and tamoxifen use.[1 4–6] Largely attributed to increased rates of obesity and greater life expectancy, rates of endometrial cancer have increased by approximately 1% per year since the mid-2000s.[4 5] The majority of cases are diagnosed at an early stage and can be successfully treated with surgery.[4] As a result, 5-year relative survival rates are generally around 80%.[3 4]

Traditional treatment of endometrial cancer varies by histology, stage, grade, and more recently, the incorporation of molecular characteristics. Currently, the treatment of localized endometrial cancer is surgery with hysterectomy and bilateral salpingo-oophorectomy with or without staging (sentinel lymph node biopsy or pelvic lymphadenectomy).[3 4 7] Adjuvant therapy with or without radiotherapy and/or chemotherapy is indicated in a small fraction of patients according to well-defined clinical-pathological-molecular risk factors.[3 7] Although the majority of patients will be diagnosed with uterine-confined and surgically manageable disease, approximately 3–13% of patients will experience disease recurrence.[8] Recurrent disease accounts for the vast majority of endometrial cancer-related deaths.[9] Outcomes of recurrent disease are poor, with a 5-year overall survival rate of 20–25%.[2]

Currently, there are limited options for the treatment of metastatic or recurrent endometrial cancer in the first-line setting, representing a significant unmet clinical need. The landscape of endometrial cancer treatment is shifting given that molecular testing can now drive treatment selection and identify patients who may be eligible for clinical trials, both in the first-line and recurrent settings. The overall goal is to give patients the best outcome while minimizing toxicity. While current recommendations include chemotherapy as first-line treatment for metastatic or recurrent endometrial cancer, emerging evidence suggests that hormonal therapy, particularly in combination with other treatment regimens guided by biomarkers, could be efficacious in selected subtypes (low-grade endometrioid carcinoma of the endometrium).

This review aims to critically evaluate recent evidence supporting hormonal therapy as a first-line, molecularly driven therapeutic option for metastatic or recurrent low-grade endometrial cancer.

Molecular and histologic subtypes of endometrial cancer

In 2013, The Cancer Genome Atlas (TCGA) Research Network proposed a molecular classification system

based on somatic mutational burden and copy-number alterations, which stratified endometrial cancers into four distinct molecular subgroups: (1) polymerase epsilon ultramutated (~7%), (2) microsatellite instability hypermutated (~30%), (3) copy-number low (~40%), and (4) copy-number high (~25%).[10]

Based on initial work in TCGA classification, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) and the Postoperative Radiation Therapy in Endometrial Carcinoma (transPORTEC) classification systems were developed.[11–14] These systems define four subgroups analogous, but not identical, to the TCGA classification system: polymerase epsilon mutated, mismatch repair deficient, p53 abnormal, and no specific molecular profile (NSMP). These surrogate markers are related to clinical outcome, and they have demonstrated prognostic value.[11] The majority of low-grade endometrioid tumors are classified as NSMP.[3 11] These tumors are polymerase epsilon wild-type, mismatch repair proficient, and p53 wild-type.[3] NSMP tumors are generally hormone receptor-positive, can have a high amount of lymph-vascular space invasion, and have an intermediate prognosis.[3 11 13 15] Importantly, NSMP has been shown to have minimal benefit from adjuvant chemotherapy; however, NSMP represents a heterogeneous group that has potential to be further broken down.[3 11] For example, this subgroup can be stratified by L1 cell adhesion molecule expression or mutations in *CTNNB1*, both of which are predictive of high-risk disease and worse outcome.[15–17] In contrast, estrogen receptor positivity and absence of lymph-vascular space invasion are associated with a more favorable prognosis, and these tumors are more likely to be sensitive to hormonal therapy.[15]

Treatment options for women with advanced disease remain broad. Integrating molecular characteristics with traditional clinicopathology may reduce overtreatment or undertreatment and help guide the appropriate choice of therapies and effective design of future studies. Accordingly, molecular classification has been incorporated into the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)*[7], the European Society for Medical Oncology (ESMO) guidelines[2], and the European Society of Gynecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society for Pathology (ESP) guidelines to aid in adjuvant treatment decisions. Recently, molecular classifications have been added to the WHO Classification of Tumors staging.[18]

NSMP subtype of endometrial cancer

Approximately 20–40% of low-grade endometrioid cancers present with deficient mismatch repair status, and only a small fraction present with polymerase epsilon mutated (<10%) or p53 abnormal (<5%) molecular profiles.[10 11 19] These tumors are distinct from high-grade tumors histologically, molecularly, and in treatment response.

NSMP cancers generally express an estrogen receptor and/or a progesterone receptor.[20] Although there is no consensus for the cut-off for estrogen/progesterone receptor positive in endometrial cancers, a recent study suggested that cases with 0–10% estrogen/progesterone receptor expression had the worst outcomes (5 year disease-specific survival =75.9–83.3%), 20–80% estrogen/progesterone receptor expression had intermediate outcomes (5 year disease-specific survival =93–93.9%), and 90–100% estrogen/progesterone receptor expression had favorable outcomes (5 year disease-specific survival =97.8%–100%).[20]

A more recent study demonstrated that estrogen receptor-positivity (defined by ≥10%) is a strong favorable prognostic factor in NSMP high-risk endometrial cancer, but not in other molecular subgroups, suggesting that incorporating estrogen receptor status of NSMP cancers could improve risk stratification.[21] Similarly, both grade and estrogen receptor-positivity (defined as ≥1%) were shown to discern high vs low risk NSMP subtypes in a large cohort study.[22] Hormonal therapies are most effective in hormone receptor-positive tumors, with a clear relationship between percent hormone receptor positivity and treatment response.[23 24]

Common pathways altered within this subtype include phosphatidylinositol-3 kinase (PI3K), mitogen-activated protein kinase (MAPK), and cyclin D1 (CCND1)- cyclin dependent kinase (CDK)4/6. Approximately 93% of endometrioid tumors harbor mutations that suggest there is potential for targeted therapy with PI3K pathway inhibitors.[10] Other common alterations in this subtype include structural aberrations in genes involved in the epidermal growth factor receptor (EGFR)-rat sarcoma virus (RAS) -MAPK pathway and alterations in the CCND1-CDK4/6 pathway, including elevated CDK4 expression.[10 25 26] Molecular information may be exploited for targeted treatment options in the recurrent setting (Figure 1).

Efficacy of chemotherapy in low-grade cancer

For patients with metastatic or recurrent extra-pelvic endometrial cancers not amenable to definitive primary surgery and/or radiation therapy, platinum-based chemotherapy is the current standard of care.[2] In 2007, a review of four Gynecologic Oncology Group (GOG) trials evaluated the relationship between histology and outcomes in patients with metastatic or recurrent endometrial cancer treated with single agent or combination chemotherapy regimens, including doxorubicin, doxorubicin/cisplatin, doxorubicin/paclitaxel, and paclitaxel/doxorubicin/cisplatin. The median overall survival was less than 12 months, and progression-free survival ranged from 3 months to 6 months based on tumor histology.[27] In the same report, patients with low-grade cancer showed a trend toward lower estimated odds of response to chemotherapy compared with those with high-grade disease (p=0.09).[27] More recently, carboplatin/paclitaxel was established as standard of care by GOG 209. This study demonstrated an overall response rate of 52%, a median progression-free survival of 13 months, and an overall survival of 37 months.[28] However, this study did not differentiate by histology and molecular subtypes. Considering biomarkers in treatment design may help to identify personalized regimens that may be more effective than conventional chemotherapy in select subsets. Although cytotoxic chemotherapy achieves higher initial response rates, treatment with chemotherapy in second-line settings is underwhelming and associated with lower response rates (10–15%), short progression-free survival (< 4 months), and substantial toxicity affecting quality of life.[3 29]

Recent data suggest that chemotherapy offers the greatest benefit for patients with p53 abnormal tumors, which includes serous tumors and a small number of other histological subtypes.[11 30] While chemotherapy is still standard of care for p53 abnormal tumors, NSMP cancers (with hormone-sensitive biomarkers) are less likely to respond to chemotherapy.[11 27] This was highlighted in the PORTEC3 trial, where patients with the NSMP molecular profile, which includes the majority of low-grade endometrioid tumors, reported limited benefit when chemotherapy

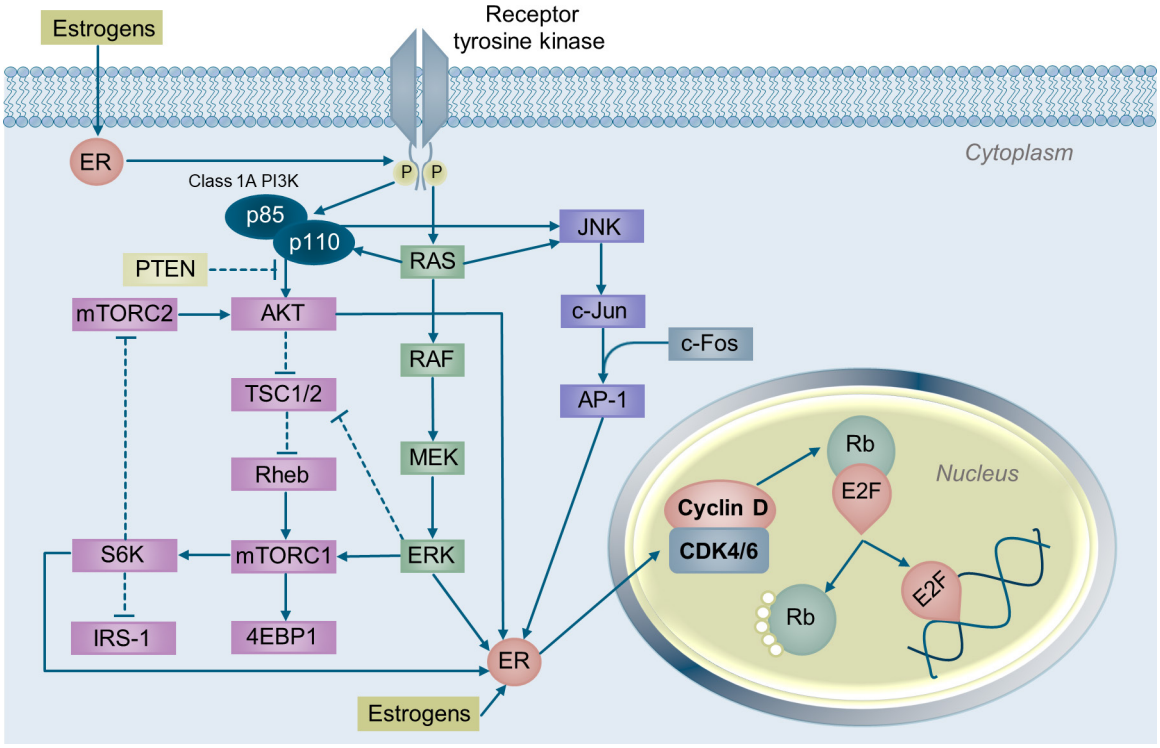

Figure 1 Cross-Talk between growth signaling pathways and estrogen receptor. Estrogen receptor signaling has multiple regulatory interactions with growth factor signaling pathways.

was added to radiotherapy in advanced stages.[11] Major guidelines include hormonal therapy as a therapeutic option for chemotherapy naïve patients with low-grade endometrioid cancer as a first-line option in the recurrent setting.[2 3 7]

Role of hormonal therapy in low-grade endometrial cancer

In advanced stage and recurrent endometrial carcinoma, response rates to hormonal therapy are up to 58% (range: 8-58%).[3 31] Patients with low-grade, hormone receptor-positive tumors are likely to respond.[3] For patients with recurrent endometrioid tumors that are hormone receptor positive, hormonal agents can be considered as first-line treatment. This is supported by both the NCCN Guidelines [(7)] and the European Society for Medical Oncology (ESMO) Guidelines,[2 3] which recommend hormonal therapy for patients with recurrent low-grade endometrioid cancer.

There are many different hormonal agents available, each with a distinct mechanism of action. Progestins and aromatase inhibitors are commonly used as standard hormonal agents in the treatment of patients with low-grade endometrial cancer in the United States and Europe.[2 3 7] In the first-line setting, hormonal therapy is associated with a mean overall response rate of 21.6% (range 0–57.1), while the second-line setting is associated with a mean overall response rate of 18.5% (range 0–53.0).[32] For patients with hormone receptor-positive disease, the overall response rate is up to 100%, while patients with hormone-receptor negative disease typically do not respond to treatment in the first-line setting.[32]

Progestins used as first-line therapy for metastatic or recurrent endometrial cancer have an overall response rate of 23.3%, a median progression-free survival of 2.9 months, and a median overall survival of 9.2 months[32], however the efficacy is not stratified by grade or hormone receptor expression status. Response to progestin therapy is higher in progesterone receptor-positive tumors with a well-differentiated histology, and recurrence after progestins generally does not extend beyond the uterus.[33 34] Use of progestin therapy has also been limited by the development of thromboembolic events.[35] However, there are still key questions to be answered regarding progestin treatment, including how to incorporate molecular markers into identifying the best candidates for progestin therapy.[36]

Selective estrogen receptor modulators, such as tamoxifen, are also suggested as a potentially effective hormonal therapy for endometrial carcinoma. Tamoxifen alone has low activity in patients with metastatic or recurrent endometrial cancer who have not received systemic therapy, and thus is not useful as a single agent.[37] Several studies have looked at the sequential use of tamoxifen and progestins. GOG 153 and GOG 119 demonstrated higher activity of the alternating regimens compared with single agent, with response rates of 27% (38% for Grade 1 tumors), and 33%, respectively, in all patients with no prior hormonal therapy or chemotherapy regardless of grade or histology.[38 39] These response rates are promising and are potentially higher if restricted to low-grade endometrial cancer as a front-line therapy, particularly in patients who have not received prior chemotherapy.

In hormone dependent tumors, anti-estrogen therapy is well established and is an acceptable treatment option included by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO). Anti-estrogen therapy with aromatase inhibitors also shows activity in select subsets of recurrent hormone receptor positive endometrial cancers. In a study of chemotherapy naïve endometrial cancer, treatment with anastrozole showed a 9% response rate in unselected patients.[40]

The Paragon trial focused on patients with hormone receptor positive recurrent endometrial cancer. The partial response rate was 7% and the clinical benefit rate was 44%.[41] Furthermore, selective estrogen receptor degraders, such as fulvestrant, are potentially useful hormonal therapies for hormone receptor positive endometrial cancers. Fulvestrant showed good activity in patients with estrogen receptor positive metastatic or recurrent endometrial cancer, with progression-free survival and overall survival of 10 and 26 months, respectively.[23] This is in contrast to estrogen receptor negative patients, who had a progression-free survival of 2 months and overall survival of 3 months in this same study. This study confirms the potential activity of anti-estrogen in well selected patient populations. Another study of fulvestrant showed lower activity (progression-free survival =2.3 months; overall survival =13.2 months); however, this study did not confirm the receptor status of the recurring tumor.[24]

Low-grade endometrioid histology tend to be hormone receptor positive tumors and are more likely to respond to endocrine therapy, especially in earlier, chemotherapy naïve settings. Hormonal therapies are an attractive therapeutic option for these types of tumors, as they have a good safety profile. Many patients with Grade 1 or 2 endometrioid cancer should be treated with hormonal therapy before the introduction of toxic chemotherapy. However, there is a need to improve the clinical efficacy of hormonal therapy to achieve better outcomes.

Hormonal therapy in chemotherapy naïve metastatic or recurrent settings

While studies of single agent hormonal therapies have demonstrated clinical benefit and prolonged progression-free survival in chemotherapy/hormonal therapy naïve patients with low-grade endometrioid cancer, responses are still limited, suggesting a need for better treatment options. Several recent and exciting studies have suggested the use of combination hormonal therapy and other targeted therapies in chemotherapy naïve patients with metastatic or recurrent hormone receptor positive endometrioid cancer. Therapies that target common alterations in endometrioid cancers in carefully selected patients have demonstrated clinical efficacy.

Pathological alterations in the PI3K/Protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, including loss of Phosphatase and tensin homolog (PTEN), occurs in 80–95% of endometrioid cancers.[10 42] However, monotherapy with mTOR inhibitors have limited activity, although activity may be higher in low-grade endometrioid tumors.[43] There is cross-talk between the PI3K/AKT/mTOR pathway and estrogen receptor (Figure 1), and deregulation of this pathway is one mechanism of hormonal therapy resistance.[42 44] Thus, studies have looked at the combination of mTOR inhibitors and endocrine therapy. In a single-arm, phase II trial, Slomovitz *et al.* demonstrated that the mTOR inhibitor everolimus in combination with letrozole results in a high clinical benefit rate and high objective response rate in patients with recurrent endometrial cancer.[44] Subsequently, GOG 3007 looked at everolimus in combination with letrozole compared with the alternating regimen of medroxyprogesterone acetate/tamoxifen. On everolimus/letrozole, chemotherapy naïve patients demonstrated a 28 month median progression-free survival, while patients who received prior chemotherapy had a 4 month median progression-free survival.[42] Progression-free survival was also higher in chemotherapy naïve patients in the medroxyprogesterone acetate/tamoxifen group (5 months vs 3 months). The results in chemotherapy naïve patients on everolimus/leterozole compares favorably to the chemotherapy trials,[27 28] and warrants further investigation into hormonal therapy combined with molecularly targeted therapies as the standard of care in carefully selected patients with anticipated benefits. Furthermore, it highlights the importance of treatment sequencing, given that hormonal therapy has a greater benefit when given before chemotherapy.

A recent phase I/II study comparing the mTOR inhibitor vistusertib combined with anastrozole to anastrozole alone demonstrated a 67.3% progression-free rate at 8 weeks among patients receiving the combination vs 39.1% in the anastrozole arm.[45] However, this study also highlighted the need to better classify metastatic or recurrent endometrial cancer as well as identify predictive biomarkers of efficacy for targeted therapy. Classification by molecular subgroups may better select for patients who would be more likely to experience favorable outcomes.

The PALEO trial is the first randomized trial to evaluate the efficacy of a CDK4/6 inhibitor, palbociclib, in combination with an aromatase inhibitor (letrozole), in patients with advanced or recurrent estrogen receptor positive endometrial cancer.[46] The combination treatment resulted in clinically meaningful progression-free survival in this phase II study. Additional phase II trials have suggested synergy for the addition of CDK4/6 inhibitors in combination with letrozole.[47 48]

The KEYNOTE 775 trial tested the combination of the multi-tyrosine kinase inhibitor lenvatinib with the checkpoint inhibitor pembrolizumab. In this trial, the median progression-free survival and overall survival for the lenvatinib/pembrolizumab arm was 6.6 months and 17.4 months, respectively, vs 3.8 months progression-free survival and 12 months overall survival for physician's choice chemotherapy.[29] This combination was recently approved for patients who have received at least one prior platinum-based chemotherapy regimen in any setting. In addition, recently reported subgroup exploratory analysis of KEYNOTE 775 reported significant benefit in overall survival and progression-free survival for lenvatinib/pembrolizumab in low-grade endometrioid tumors.[49]

Hormone receptor positive breast and low-grade serous ovarian cancers

Low-grade, hormone receptor-positive subtypes of endometrial cancer are similar to breast cancer in that they are hormone driven. However, studies have reported limited activity of single agent aromatase inhibitors. Given this limited activity, strategies to improve aromatase inhibitor efficiency have been extensively studied in metastatic breast cancer, and it is likely that similar benefits may be seen in patients with endometrial cancer.

Cell cycle regulation, specifically at the Gap 1 to synthesis phase transition, is critical for committing cells to proliferation.[50] CDK4/6 inhibition has been demonstrated to synergize with anti-estrogen therapy. Combination studies of palbociclib and anti-estrogen therapy demonstrated increased activity against estrogen receptor positive breast cancer,[51 52] leading to regulatory approval of palbociclib in combination with letrozole for use in hormone receptor positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer. In previously untreated estrogen receptor positive breast cancer, the combination of palbociclib and letrozole is superior to letrozole alone, with a

median progression-free survival of 24.8 months vs 14.5 months, respectively.[52] More recently, ribociclib in combination with endocrine therapy was shown to significantly increase overall survival among patients with advanced hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer[53], and abemaciclib in combination with fulvestrant was shown to significantly increase overall survival.[54] Phase II studies in endometrial cancer have suggested similarly promising results from combining endocrine and targeted therapies,[42 46 47] although no phase III studies have been completed.

Similarly, hormonal therapy has become the main focus in low-grade serous ovarian cancer, which is often hormone receptor positive and responds poorly to chemotherapy.[55–57] Currently, there are ongoing trials investigating the role of first-line hormonal therapy with letrozole compared with chemotherapy followed by letrozole, as well as trials investigating the efficacy of hormonal therapy combined with novel therapies such as CDK4/6 inhibition.[58–60]

Interestingly, recent studies in breast and ovarian cancer have suggested correlation of estrogen receptor signal transduction pathway activity, as opposed to expression, with both response to and progression-free survival after hormonal therapy, independent of receptor expression levels.[61 62] Similarly, a recent study found estrogen receptor signal transduction pathway activity to be a prognostic marker of response to hormonal therapy in endometrial cancer.[63] It is therefore possible that pathway activity could be tested in the future as a predictive biomarker as a response to hormonal therapy.

These studies highlight the need for hormonal therapy approaches combined with novel therapeutics to target mechanisms of resistance. The ultimate goal is to increase response and durability in low-grade endometrioid cancer patients, while at the same time limiting toxicity and improving quality of life.

CONCLUSIONS

Hormonal therapy offers many benefits, including oral dosing and fewer side effects. Hormonal therapy is better tolerated in the acute phase, and there is opportunity for longer exposure given the lack of chronic toxicity. If there is progression after hormonal therapy, patients would still be eligible for other trials, and use of hormonal therapy does not preclude the use or limit the benefits of future chemotherapy.

Chemotherapy results in higher objective response rates compared with hormonal therapy alone, highlighting the need to combine hormonal therapy with other treatment options. Given the promising results of phase II studies, as well as studies in breast cancer, molecularly informed targeted therapy in combination with hormonal therapy has the potential to provide better options for patients with metastatic or recurrent endometrioid cancer. Further refinement of molecular subgroups, specifically NSMP, will help to select patients most likely to benefit from these therapies as these subgroups are incorporated into molecularly directed trials and treatment recommendations.

In the past, the GOG initiated trials evaluating chemotherapy versus hormone therapy in the first-line management of disease (GOG 199). Due to clinician preference for chemotherapy, the trial was halted. Enthusiasm for biomarker therapies will lead to the inclusion of molecular classification in future trials. Future clinical trials should not look at heterogeneous populations, but rather specific adjuvant therapies in specific subtypes. Immunotherapies and biomarker directed therapies with checkpoint inhibitors as first-line therapies in endometrial cancers will carry over in trials of other therapies.

Author affiliations
[1]Department of Obstetrics and Gynecology, Women's Health Institute, Cleveland Clinic, Cleveland, Ohio, USA
[2]Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA
[3]Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire (GINECO), Centre Leon Berard, Lyon, Rhône-Alpes, France
[4]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[5]Catholic University of the Sacred Heart, Rome, Italy
[6]Department of Oncology, Rigshospitalet, Kobenhavn, Denmark
[7]HonorHealth Research Institute, University of Arizona, Creighton University, Phoenix, Arizona, USA
[8]Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, Florida, USA

Twitter Brian Slomovitz @gyncancermd

Contributors All authors provided substantial contribution to the conception, review, and revision of the manuscript. All authors approve of and agree to be accountable for all aspects of the work. Medical writing support was provided by Laura Bisogno, PhD; Julie Hurt, PhD, and Jenni Pickett, PhD of Whitsell Innovations, Inc. Chapel Hill, NC, USA.

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ORCID iDs
Isabelle Ray-Coquard http://orcid.org/0000-0003-2472-8306
Bradley J Monk http://orcid.org/0000-0001-6985-0159
Brian Slomovitz http://orcid.org/0000-0002-7241-3096

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