REVIEW

Recent advances in endometrial cancer: a review of key clinical trials from 2015 to 2019 [version 1; peer review: 2 approved]

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Abstract
In the past few years, we have seen several important advances in understanding of and therapy for endometrial cancer. This review highlights key recent abstracts and publications in endometrial cancer from 2015 to 2019. We focus on clinical trials in surgical staging and the utility of sentinel lymph node mapping, adjuvant treatment for high-risk disease and HER2/neu-positive serous tumors, combination therapy for recurrent disease, molecular biology, and immunotherapy.

Keywords
uterine cancer, endometrial cancer

Open Peer Review

Reviewer Status ✔ ✔
Invited Reviewers
1 2
version 1 published 12 Jun 2019

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Author roles: Charo LM: Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Plaxe SC: Conceptualization, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Charo LM and Plaxe SC. Recent advances in endometrial cancer: a review of key clinical trials from 2015 to 2019 [version 1; peer review: 2 approved] F1000Research 2019, 8(F1000 Faculty Rev):849 (https://doi.org/10.12688/f1000research.17408.1)

First published: 12 Jun 2019, 8(F1000 Faculty Rev):849 (https://doi.org/10.12688/f1000research.17408.1)
Introduction
In 2019, there will be an estimated 61,880 new cases of and 12,160 deaths from endometrial cancer1. It is the most common gynecologic malignancy in the US and the only gynecologic cancer with increasing incidence and mortality2. Tran and Gehrig published a comprehensive F1000 Faculty Review in January 20173. They outlined the genetic bases of endometrial cancer, novel surgical treatment, molecular targeted therapeutics, and current clinical trials. We invite you to reference their review for the groundwork of this article. Since their publication, we have seen several important advances in understanding and therapy, including surgical staging and the utility of sentinel lymph node (SLN) mapping, adjuvant treatment for high-risk disease and HER2/neu-positive serous tumors, combination therapy for recurrent disease, molecular biology, and immunotherapy. We focus on these recent advances.

Surgical staging: sentinel lymph node evaluation
Lymph node involvement is a critical factor in determining prognosis and adjuvant therapy in endometrial cancer. As discussed in greater detail below, evidence supports a survival advantage for adjuvant chemotherapy in patients with stage III endometrial cancer; however, a similar benefit may not accrue to patients with locally advanced disease4–6. Complete staging lymphadenectomies have been associated with morbidity that impacts quality of life, including lymphedema, lymphocele formation, and neuralgia7,8. Several criteria have been proposed to define patients in whom the risk is low enough to safely omit a staging lymphadenectomy. Most recently, the Korean Gynecologic Oncology Group showed that their criteria—endometrioid histology, no evidence of deep invasion or enlarged lymph nodes on magnetic resonance imaging (MRI), and preoperative CA-125 of less than 35 units/mL—resulted in a negative predictive value of 97.1%; however, some criticize the cost and burden associated with obtaining pre-operative MRI and CA-1259. SLN biopsies offer a compromise and have been shown to reduce risks of lymphedema and lymphocele10.

In 2017, the results of the Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial were published11. This large, multicenter, prospective cohort study enrolled patients with clinical stage I endometrial cancer and determined the sensitivity and negative predictive value of SLN mapping in detecting metastatic disease compared with the gold standard complete lymphadenectomy. FIRES investigators injected indocyanine green into the cervix and performed SLN mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Pathologists assessed SLNs for metastases by hematoxylin and eosin (H&E) staining. If the results were negative by H&E, they performed cytokeratin immunohistochemistry (IHC) ultra-staging. They found an impressive 97% sensitivity and 99.6% negative predictive value11.

In the FIRES trial, approximately 14% of patients did not map and approximately 34% of patients mapped to only one side, which would necessitate approximately 48% of patients to have a lymphadenectomy due to mapping failure. Conversely, over half of patients with endometrial cancer can be spared a complete staging lymphadenectomy with SLN mapping. Some have raised concerns regarding missing isolated para-aortic metastases in SLN mapping12, especially in those with the highest prevalence of para-aortic metastases (high-grade and deeply invasive tumors)13. One study showed that SLN biopsies detected more metastatic nodal disease compared with selective pelvic and para-aortic lymphadenectomies14. This was recently confirmed in a meta-analysis of 3,536 patients in six studies, showing higher positive pelvic nodal detection rates, no difference in para-aortic nodal detection rates, and no difference in overall recurrence or nodal recurrence rates in SLN compared with complete lymphadenectomy15. Additionally, the risk of para-aortic recurrence in patients with positive pelvic nodes and unassessed para-aortic nodes is only 4%16. In regard to high-risk histology, a prospective study examined women with grade 3 (endometrioid, serous, clear cell, and carcinosarcoma) endometrial cancer by SLN biopsy followed by full pelvic and para-aortic lymphadenectomy; they found 95% sensitivity and 98% negative predictive value and bilateral mapping rates of 58% and unilateral mapping rates of 40%, supporting the use of SLN in high-risk patients17. Additionally, 27% of patients in the FIRES trial and 27 to 100% of patients in the six studies included in the meta-analysis had high-grade histology18.

In order to adequately evaluate nodal status, patients who do not map to one or both sides should have unilateral or bilateral complete lymphadenectomies, respectively. Additionally, all enlarged or suspicious lymph nodes should be removed, regardless of SLN mapping18. According to the Society of Gynecologic Oncology (SGO) Clinical Practice Statement, individual surgeons should consider performing full lymphadenectomy while their personal experience is accrued (20 to 30 cases) to ensure that they, and their pathologists, demonstrate acceptable sensitivity and negative predictive value. The decreased morbidity, high sensitivity, and high negative predictive value make SLN evaluation an appealing and standard option, which is supported by both the National Comprehensive Cancer Network (NCCN) and the SGO; however, some surgeons may choose to limit its use to intermediate-risk populations until further data accrue. Additionally, data to guide adjuvant treatment (that is, adding extended-field radiation) in patients with positive pelvic lymph nodes with unknown para-aortic nodal status are needed.

Adjuvant treatment for high-risk endometrial cancers
Most endometrial cancers will be cured with surgery alone. However, many advanced-stage and some early-stage cancers will recur. Multiple studies have characterized the risk of post-surgical recurrence and tried to identify adjunctive therapies to reduce it. High-risk factors include tumor grade, tumor size, cell type, depth of myometrial invasion, presence of lymphovascular space invasion (LVSI), and stage19,20–21. Because of randomized controlled trials and retrospective series comparing adjuvant chemotherapy with radiation therapy, there has been optimism
that chemotherapy may reduce the risk of distant recurrence and improve survival for patients with high-risk disease. However, as outlined below, chemotherapy has shown improvement in overall survival (OS) in advanced-stage disease but not in high-risk, early-stage patients. Radiation therapy is known to be quite effective in achieving local control, but improvement in OS has not been realized\(^\text{19,20,22,23}\). Recently, the results of three important trials that evaluated combined radiation and chemotherapy aimed at reducing rates of both local and distant recurrence were presented: the results of GOG 249 were published in the *Journal of Clinical Oncology* in April 2019\(^\text{24}\), Gynecologic Oncology Group (GOG) protocol 258 was presented in abstract form\(^\text{25}\), and the results of Post-Operative Radiation Therapy in Endometrial Carcinoma 3 (PORTEC 3) were published in *Lancet Oncology* in March 2018\(^\text{26}\). GOG 249 investigated the role of adjuvant chemotherapy and vaginal brachytherapy in early-stage, high-risk patients\(^\text{24}\), whereas GOG 258\(^\text{24-26}\) and PORTEC 3\(^\text{24-26}\) examined the role of combined chemotherapy and radiation in high-risk cohorts. Table 1 outlines the details of these and other key trials that guide adjuvant therapy in high-intermediate and high-risk endometrial cancer.

### Stage I and II endometrioid endometrial cancers

Certain subgroups of early-stage endometrial cancer have a high risk of recurrence. Based on the large factors identified in GOG 33, a subgroup was identified in GOG 99 as “high-intermediate risk”\(^\text{19}\). This cohort accounted for two thirds of recurrences and cancer-related deaths. From these studies, the GOG 249 investigators identified a population of high-risk, early-stage endometrial cancer patients who may benefit from aggressive adjuvant therapy\(^\text{27}\). Investigators compared vaginal cuff brachytherapy combined with chemotherapy to pelvic radiation. This was the first GOG study to include intensity-modulated radiation therapy. After a median follow-up of 53 months, they found that chemoradiation did not improve progression-free survival (PFS) and patients receiving chemotherapy experienced more adverse events. There were no differences in vaginal or distant failure rates; however, pelvic and para-aortic nodal failures were more common among patients who received vaginal cuff brachytherapy with chemotherapy. Of note, a subset analysis of patients with serous or clear cell tumors did not find a benefit in PFS or OS with vaginal cuff brachytherapy combined with chemotherapy.

The PORTEC 3 trial, discussed in further detail below, also included high-risk, early-stage endometrioid endometrial cancers (stage I grade 3 endometrioid cancers with deep myometrial invasion or LVSI and stage II endometrioid cancers). This study compared chemoradiation to whole pelvic radiation and did not find significant improvement in failure-free survival (FFS) (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.47–1.33) or OS (HR 0.77, 95% CI 0.49–1.21) to justify the addition of chemotherapy in stage I or II endometrioid cancers\(^\text{26}\).

Given increased toxicity without PFS or OS benefit, we would recommend against chemotherapy for high-risk stage I and II endometrioid endometrial cancers. Radiation should be considered for local control. Given the results of the PORTEC trials\(^\text{21,22,25,26}\), it would be reasonable to offer external beam radiation therapy (EBRT) for grade 3 endometrioid cancers with deep myometrial invasion or LVSI or both. Other high-intermediate risk endometrioid cancers can be treated with adjuvant vaginal cuff brachytherapy\(^\text{22,23,27}\).

### Advanced endometrioid endometrial cancers

Defining the optimal post-operative adjuvant treatment for advanced endometrial cancer remains challenging. There is increased risk of distant failure in patients who receive radiation alone and increased pelvic failures in patients who receive chemotherapy alone. GOG 122 showed a PFS and OS benefit with chemotherapy (doxorubicin 60 mg/m\(^2\) and cisplatin 50 mg/m\(^2\) every three weeks for seven cycles, followed by one cycle of cisplatin) compared with whole abdomen radiation therapy in patients with stage III to IVA with less than 2 cm post-operative residual disease\(^\text{6}\).

Given the concern for increased pelvic relapse with adjuvant chemotherapy alone in high-risk endometrial cancer, the phase II RTOG-9708 trial assessed the toxicity of adjuvant combined chemoradiation and chemotherapy in grade 2 or 3 endometrial adenocarcinoma with outer one half myometrial invasion, cervical stromal invasion, or pelvic-confined extraterine disease\(^\text{28}\). The trial showed promising locoregional control (4-year disease-free survival 85% and OS 81%) with adjuvant cisplatin 50 mg/m\(^2\) intravenously at days 1 and 29 plus volume-directed radiation therapy (45 Gy ± brachytherapy) followed by paclitaxel 175 mg/m\(^2\) and carboplatin area under the curve (AUC) 5 every 21 days for four cycles. Given their success and the theoretical benefit of obtaining both local and distant control with combined chemotherapy and radiation, GOG 258 and PORTEC 3 used similar regimens in their experimental arms. Since the last review, the results of GOG 258 have been presented and published in abstract form, and the results of PORTEC 3 have been published\(^\text{25,26}\).

GOG 258 compared chemoradiation followed by four cycles of paclitaxel/carboplatin to six cycles of paclitaxel/carboplatin alone (Table 1)\(^\text{25}\). The combined arm had fewer vaginal, pelvic, and para-aortic recurrences and more distant recurrences and toxicity; however, there was no improvement in PFS or OS. PORTEC 3 compared chemoradiation plus chemotherapy with whole pelvic radiation alone in patients with high-risk stage I to III endometrial cancer (Table 1)\(^\text{26}\). The investigators found that the addition of chemotherapy improved FFS but did not result in a significant improvement in OS. A subgroup analysis of stage III patients showed the greatest FFS advantage (HR 0.66, 95% CI 0.45–0.97) with a non-significant trend toward improved OS (HR 0.71, 95% CI 0.45–1.11). The results of these large phase III studies did not identify a clear best option for adjuvant therapy; however, it may be extrapolated that adjuvant chemotherapy is most important for stage III patients.

In summary, in regard to the latest studies, adjuvant chemotherapy likely has the most benefit in stage III and IV patients.
### Table 1. Key trials guiding adjuvant therapy in high-intermediate and high-risk endometrial cancer.

| Trial | Years of accrual | Number of patients assessed | Eligibility | LN assessed | Arms | Aims | Outcomes | Conclusions |
|-------|-----------------|----------------------------|-------------|-------------|------|------|----------|-------------|
| PORTEC | 1990–1997 | N = 714 | Stage I: IB G2–3, IC G1–2 | No | Observation versus WPRT (46 Gy) | Primary: Locoregional recurrence and death | -5-year locoregional recurrence: 14% obs versus 4% WPRT (P <0.001) | Adjuvant RT improves locoregional control, not OS |
| Creutzberg et al. (2000) | | | | | | Secondary: Treatment-related morbidity and survival after relapse | -5-year OS: 85% obs versus 81% WPRT (P = 0.31) | -Limit adjuvant RT to patients age > 60 with G3 and less than half myometrial invasion or any grade with outer half myometrial invasion |
| | | | | | | -Cancer-related death: 6% obs versus 9% WPRT (P = 0.37) | -Avoid adjuvant RT if age < 60 or G2 with superficial invasion (risk locoregional recurrence < 5%) |
| | | | | | | -Treatment-related complications: 6% obs versus 25% WPRT (P <0.001) | -15-year follow-up study: confirms. Limit adjuvant pelvic RT to HIR cohort |
| | | | | | | 2-year survival after recurrence: 79% after vaginal versus 21% after pelvic/distant recurrence | |
| | | | | | | 15-year follow-up: locoregional recurrence 15.5% obs versus 6% WPRT |
| GOG 99 | 1987–1995 | N = 392 | "Intermediate risk:" IB IC II (occult) | Yes | Observation versus WPRT (50.4 Gy) | Primary: Toxicity, date and location of recurrence, OS | -Authors defined a HIR group by age and number of RFs: | |
| Keys et al. (2004) | | | | | | RF: grade 2–3, LVSI, and outer 1/3 | |
| | | | | | | Age | # RF |
| | | | | | | <50 | 3 |
| | | | | | | 50–69 | 2 |
| | | | | | | >70 | 1 |
| | | | | | | In all patients: | |
| | | | | | | -2-year cumulative incidence of recurrence: 12% obs versus 3% WPRT (RH: 0.42, P = 0.007) | |
| | | | | | | -18 versus 3 vaginal recurrences | |
| | | | | | | -OS: 86% obs versus 92% WPRT (RH: 0.86, P = 0.557) | |
| | | | | | | In the HIR group: | |
| | | | | | | -2-year recurrence: 26% obs versus 6% WPRT | |
| PORTEC-2 | 2002–2006 | N = 427 | Age > 60 IB G3 IC G1 or 2, IIA (any age, exclude G3 with outer half invasion) | No | EBRT (46 Gy in 23 fx) versus VCB (21 Gy HDR in 3 fx or 30 Gy LDR) | Non-inferiority trial | -5-year vaginal recurrence rate: 1.8% VCB versus 1.6% EBRT (HR 0.78, 95% CI 0.71–3.49, P = 0.74) | VCB is non-inferior to WPRT in this HIR group, with fewer gastrointestinal toxic effects |
| Nout et al. (2010) | | | | | | Primary: Vaginal recurrence | -5-year locoregional relapse: 5.1% VCB versus 2.1% EBRT (HR 2.08, 95% CI 0.71–6.08, P = 0.17) | |
| | | | | | | -OS: 84.8% VCB versus 79.6% EBRT (HR 1.17, 95% CI 0.69–1.98, P = 0.67) | -Of note, LVSI not considered |
| | | | | | | -Rates grade 1–2 gastrointestinal toxicity: 12.6% VCB versus 53.8% WPRT | |

Note: HIR = high-intermediate risk; OS = overall survival; EBRT = external beam radiotherapy; VCB = vaginal brachytherapy; WPRT = whole pelvic radiation therapy; LVSI = lymphovascular space invasion; RF = risk factor; CI = confidence interval; HR = hazard ratio; LDR = low dose rate; HDR = high dose rate; RH = relative hazard.
| Trial | Years of accrual | Number of patients assessed | First author | Publication year | Eligibility | LN assessed | Arms | Aims | Outcomes | Conclusions |
|-------|-----------------|---------------------------|--------------|-----------------|-------------|-------------|------|------|---------|-------------|
| GOG 249 | 2009–2013 | N = 601 | Randall et al. (2019) | I with HIR criteria: RF: Outer 1/2, Grade 2 or 3, LVSI | Optional: 89% assessed | Pelvic RT (4 field or IMRT, 45 to 40.5 Gy over 5–6 weeks) Additional VCB optional for S/CC or II) | Primary: RFS Secondary: OS, patterns of failure, toxicity | -60-month RFS: 0.76 RT (95% CI 0.70–0.81) versus 0.76 VCB/C (95% CI 0.70–0.81) -60-month OS: 0.87 RT (95% CI 0.83–0.91) versus 0.85 VCB/C (95% CI 0.81–0.90) -No difference in vaginal or distant failures -5-year pelvic and para-aortic nodal failures: 9% VCB/C versus 4% RT, HR 0.47 -5-year vaginal recurrence: 2.5% versus 2.5% -5-year distant recurrence: 18% versus 18% -Toxicity: > Grade 3 acute toxicity: 11% RT versus 64% VCB/C > Grade 3 late toxicity: 13% RT versus 12% VCB/C -At 11 weeks, VCB/C arm had 3.7 points lower (98.3% CI -5.9–1.6, P <0.001) on FACIT fatigue subscale score than RT arm. RT arm returned to baseline at 11 weeks and VCB/C arm returned to baseline at 8 months -VCB/C arm reported more neurotoxicity than RT arm, however returned to baseline at 14 months -VCB/C did not improve RFS or OS compared with RT -In subgroup analysis (including serous and clear cell), VCB/C did not improve RFS or OS -Pelvic and para-aortic nodal failures more common in VCB/C -Acute mild/moderate toxicities greater in VCB/C arm, while late toxicities similar versus RT -Pelvic radiation preferred for high-risk, early-stage endometrial carcinoma |
| Locally advanced | | | | | | | | | |
| GOG 122 | 1992–2000 | N = 396 | Randall et al. (2006) | III/IV (post-op residual disease < 2 cm) | Optional: 86% assessed | WART (30 Gy in 20 fx, with a 15-Gy boost) versus doxorubicin 60 mg/m² and cisplatin 50 mg/m² Q 3 weeks × 7 cycles, followed by 1 cycle of cisplatin (AP) | Primary: PFS Secondary: OS | Stage-adjusted progression: HR 0.71, 95% CI 0.55 to 0.91; P <0.01 Local recurrence: 13% WART versus 18% AP Distant recurrence: 38% WART versus 32% AP 5-year stage-adjusted disease-free survival: 50% CT versus 38% WART 5-year stage-adjusted OS: 55% AP versus 42% WART | -Chemotherapy improved PFS and OS compared with WART |
| Trial          | Years of accrual | Eligibility                                      | LN assessed | Arms                                                                 | Aims                                      | Outcomes                                                                 | Conclusions                                                                 |
|---------------|------------------|-------------------------------------------------|-------------|----------------------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| PORTEC-3      | 2006–2013        | IA G3 with LVSI and IB G3                       | Optional: 58% assessed | Pelvic RT (48.6 Gy in 1.8 Gy fx) versus combination chemotherapy and radiation (CTRT) (cisplatin 50 mg/m² weeks 1 and 4 of RT, followed by carboplatin AUC 5 and paclitaxel 175 mg/m² Q 3 weeks x 4 cycles) | Primary: OS and FFS | -5-year OS: 81.8% CTRT versus 76.7% RT (HR 0.76, 95% CI 0.54–1.06; P = 0.11)  
-5-year FFS: 75.5% CTRT versus 68.8% RT (HR 0.71, 95% CI 0.53–0.95; P = 0.022)  
> Grade 3 adverse events: 60% CTRT versus 12% RT  
Subgroup analysis of stage III patients:  
-5-year FFS 69.3% CTRT versus 58% RT (HR 0.66, 95% CI 0.45–0.97)  
-5-year OS 78.7% CTRT versus 69.8% RT (HR 0.71, 95% CI 0.45–1.11) | -CTRT did not improve OS, although it did increase FFS  
-Subgroup analysis of stage III: improved 5-year FFS (HR 0.66) and trend toward improved OS |
| GOG 258       | 2009–2014        | III–IVA (<2 cm residual disease) and I–II S/CC with positive washings | Optional: (% N/A) | Cisplatin 50 mg/m² intravenous D1 and D29 plus volume-directed RT (45 Gy ± brachytherapy) followed by carboplatin AUC 5/ paclitaxel 175 mg/m² Q 21 days x 4 cycles with G-CSF support (CRT) versus Carboplatin AUC 6/ Paclitaxel 175 mg/m² Q 21 days x 6 cycles (CT) | Primary: RFS  
Secondary: survival, toxicity, quality of life | -Vaginal recurrence: 3% CRT versus 7% CT (HR = 0.36, 95% CI 0.16–0.82)  
-Pelvic and para-aortic node recurrence: 10% CRT versus 21% CT (HR 4.2, 95% CI 0.28–0.66)  
-Distant recurrence: 28% CRT versus 21% CT, HR 1.36, 95% CI 1–1.86)  
-6-year recurrence-free survival: 35.7% CRT versus 38.0% (HR 0.9, 95% CI 0.74–1.1)  
> Grade 3 toxicity: 58% CRT versus 63% CT  
-Survival and quality of life endpoints not yet reported | -Chemoradiation did not improve RFS compared with chemotherapy (HR = 0.9, 95% CI 0.74–1.1)  
-More acute toxicities in CRT versus CT  
-Fewer vaginal, pelvic, and para-aortic failures in CRT versus CT  
-Distant recurrences more common in CRT than CT |

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1998 FIGO (International Federation of Gynaecology and Obstetrics) surgical staging: IA: tumor limited to endometrium; IB: tumor invasion less than one half of the myometrium, IC: tumor invasion more than half of the myometrium. II: cervical involvement (including endocervical glandular involvement and cervical stromal invasion).

Grade 1 (G1) ≤ 5% non-squamous or non-morular solid growth pattern; grade 2 (G2) 6–50% non-squamous or non-morular solid growth pattern; and grade 3 (G3): >50% non-squamous or non-morular solid growth pattern.

AP, doxorubicin/cisplatin; AUC, area under the curve; CC, clear cell; CI, confidence interval; CRT, conformal radiation therapy; CT, computed tomography; CTRT, chemotherapy and radiation therapy; EBRT, external beam radiation therapy; FACIT, Functional Assessment of Chronic Illness Therapy; FFS, failure-free survival; fx, fraction; GOG, Gynecologic Oncology Group; Gy, gray; obs, observation; HDR, high-dose radiation therapy; HIR, high-intermediate risk; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; LDR, low-dose radiation therapy; LN, lymph node; LVSI, lymphovascular space invasion; MRI, magnetic resonance imaging; N/A, not available; OS, overall survival; PFS, progression-free survival; PORTEC, Post-Operative Radiation Therapy in Endometrial Carcinoma; Q, every; RF, risk factor; RFS, recurrence-free survival; RH, relative hazard; RT, radiation therapy; S, serous; VCB, vaginal cuff brachytherapy; WART, whole abdominal radiation therapy; WPRT, whole pelvic radiation therapy.
Radiation therapy can be considered for local control. The NCCN recommends systemic therapy with or without vaginal brachytherapy or EBRT with or without vaginal brachytherapy with or without systemic therapy for adjuvant therapy of advanced-stage endometrial cancer.39

Serous and clear cell endometrial cancers

Uterine serous carcinoma is an aggressive and less common type of endometrial cancer, comprising only 3 to 10% of endometrial cancers but accounting for 39% of endometrial cancer deaths.40 Its molecular profile differs from that of type 1 endometrioid histologies; it has a high rate (90%) of TP53 alterations and about a 30% rate of HER2/neu alterations.31,32 High rates of extratumoral spread are common at presentation; 40 to 70% of cases of metastatic disease may be apparent only with comprehensive surgical staging.33 The GOG typically requires that tumors classified as serous have more than 50% serous histology if a tumor is of mixed cell type.34 However, a study by Boruta et al. demonstrated that even serous tumors with a minor component (<10%) had poorer prognosis compared with grade 3 pure endometrioid histology.35

Clear cell endometrial cancers represent about 4% of all uterine tumors and similarly have high rates of occult metastases (40%) and poor survival (40% 5-year survival regardless of stage).36 About 30 to 40% of clear cell carcinomas have TP53 alterations.37 They are intermediate in microsatellite instability (MSI) frequency (15%) and phosphatase and tensin homolog (PTEN) alterations (30%) compared with endometrioid (20 to 40% MSI and 10% PTEN alterations) and serous (<5% MSI and 35 to 50% PTEN alterations) carcinomas.38 The literature to support definitive recommendations for adjuvant treatment for serous and clear cell uterine cancers is limited because they are relatively rare. Patients with serous and clear cell histology are often included in heterogeneous trials of high-risk uterine cancers. In trials discussed above, GOG 249 included patients with stage I or II serous and clear cell uterine cancer with negative cytology; GOG 258 included stages I or II with positive cytology and stages III or IV; and PORTEC 3 included patients with stages I to III serous or clear cell cancers. It is difficult to draw conclusions regarding treatment since these histologies usually compose less than 20% of the cohort.3,21,26 Because of their aggressive nature, uterine serous and clear cell carcinomas with any myometrial invasion are often treated with adjuvant chemotherapy. The NCCN guidelines recommend chemotherapy with or without vaginal brachytherapy for IA serous or clear cell endometrial cancers, although they offer observation or EBRT as acceptable alternatives. For IB (or greater) disease, they recommend chemotherapy with or without EBRT with or without vaginal brachytherapy.20

HER2/neu-positive serous endometrial cancers

Fader et al. published their randomized phase II trial of paclitaxel and carboplatin with or without trastuzumab in primary stage III or IV or recurrent HER2/neu-positive uterine serous carcinomas.39 They randomly assigned 61 patients and found a median PFS of 12.6 months in the paclitaxel, carboplatin, and trastuzumab arm versus 8.0 months in the paclitaxel and carboplatin alone arm. In the 41 patients with primary advanced-stage disease, the PFS was 17.9 months in the trastuzumab arm versus 9.3 months in the paclitaxel/carboplatin alone arm. In the 17 patients with recurrent disease, PFS was 9.2 months in the trastuzumab arm versus 6 months in the paclitaxel/carboplatin arm. There is a suggestion of an OS advantage in the trastuzumab arm, and the greatest benefit is in the up-front setting, but the data are not yet mature. These preliminary findings are of considerable interest and suggest benefit for up-front HER2/neu tumor profiling to guide adjuvant therapy of this difficult disease.

Treatment of recurrent endometrial cancers

Systemic recurrence of endometrial cancer is generally considered incurable and is associated with a poor prognosis. A variety of GOG studies have looked at single agents (etoposide, paclitaxel, dactinomycin, liposomal doxorubicin, pyrazolocacridine, topotecan, oxaliplatin, ifosfufin, flavopiridol, and bevacizumab) and alternating courses of megestrol acetate and tamoxifen in recurrent endometrial cancer, and response rates range from 0 to 31% and 6-month PFS rates from 0 to 43%.16-46 Hormonal therapy is an appealing option in recurrent endometrial cancer given that many endometrial cancers are hormonally driven and the relative lack of toxicity with hormonal therapy. However, response rates and PFS have been disappointing. Given cross-regulation between the estrogen receptor (ER) and PI3K/AKT/mTOR pathway and recent success of combination everolimus and an aromatase inhibitor in aromatase-refractory breast cancer, Slomovitz et al. hypothesized that combining everolimus and letrozole would result in improved response rates and PFS. In their phase II study, they found a clinical benefit rate of 40%, and 23% of patients obtained a complete response. The authors found that their oral regimen of everolimus 10 mg daily with letrozole 2.5 mg daily was well tolerated, and no patients discontinued the study because of toxicity. Metformin use and CTNNB1 mutations were associated with increased response rates, PFS, and OS, although these findings were not statistically significant. Of note, none of the patients (n = 7) with serous histology had a response. Patients with ER-positive and progesterone receptor (PR)-positive tumors had higher response rates than receptor-negative tumors, although 33% of ER-negative patients and 25% of PR-negative patients had responses. Given these promising results, the investigators evaluated this combined regimen compared with alternating megestrol acetate and tamoxifen in GOG 3007, which was recently published as an abstract. They reported a 24% response rate in the everolimus/letrozole arm (PFS 6.4 months and OS 20.0 months) and a 22% response rate in the progesterone arm (PFS 3.8 months and OS 16.6 months). Hormonal combined therapies remain appealing options for recurrent endometrial cancer, and biomarkers are needed to better predict which patients will benefit.

Understanding the molecular biology of endometrial cancer

Advances in our classification of endometrial cancer with molecular profiling may enable us to better stratify risk and...
recommended therapy. MSI and polymerase-ε (POLE) lead to neoantigens, fragments of proteins expressed by tumor cells that may sensitize the immune system\(^5\). The molecular profile of a tumor may better define its prognosis and response to therapy than histology and stage alone. Talhouk et al.\(^3\)–\(^5\), The Cancer Genome Atlas Collaborative (TCGA)\(^5\)–\(^8\), and the GOG 210 investigators\(^8\)–\(^10\) have developed different molecular classification schema to better stratify patient risk.

The TCGA project determined four molecularly defined subgroups of endometrial cancer, which yielded excellent prognostic results\(^8\). However, the methods required for classification are currently quite expensive and require special handling of the tissue, limiting applicability. Talhouk et al. developed a more pragmatic method, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification, to identify molecularly distinct subgroups with a prognostic signature similar to that of the TCGA classification scheme\(^4\)–\(^6\). The four groups were MMR-deficient (MMR-D), POLE exonuclease domain mutations (POLE EDMs), p53 abnormal, and p53 wild-type. They assessed tumors in a step-wise fashion. The first assessment was based on MMR status, and MMR-D tumors were classified as MMR-D and MMR intact tumors were tested for POLE mutations. POLE mutants were classified as POLE EDM, and POLE wild-type tumors were assessed for p53 status. MMR intact, POLE wild-type tumors were classified as p53 wild-type or p53 abnormal (null/missense mutations). They validated the ProMisE classifier in a large confirmation cohort and found that POLE EDMs had the best prognosis and p53 mutants the worst. The ProMisE classification system improved outcome prediction compared with European Society for Medical Oncology risk stratification, detecting those at risk for Lynch syndrome and potentially guiding clinical management\(^6\).

GOG 210, an NRG Oncology/GOG study of the molecular classification for risk prediction in endometrioid endometrial cancer, was published in *Gynecologic Oncology* in August 2017\(^9\). The investigators sought to develop a classification system for endometrioid endometrial cancers, the most common and potentially challenging endometrial cancer histology to classify. They assessed tumors for mismatch repair (MMR) defects (MSI, MMR IHC, and MLH1 methylation), POLE mutations, and loss of heterozygosity. Using four classifications (MMR deficient, copy number altered (CNA), copy number stable, and POLE mutant), they were able to stratify patients by PFS and OS. Their classification system remained statistically significantly related to clinical outcomes in multivariable analyses. CNA had the worst PFS and cancer-specific survival, whereas the POLE group had the best outcomes. The authors advocate prospective validation of this system and recommend that clinicians consider using it to universally screen for Lynch syndrome and identify additional prognostic information to guide treatment decisions.

Biomarkers and molecular alterations are increasingly being used to guide systemic therapy in the recurrent setting. Table 2 outlines common biomarkers in endometrial cancer, noting differences between type I (grade 1 or 2 endometrioid) and type II (grade 3 endometrioid, serous, clear cell, and carcinosarcoma) endometrial cancers as well as potential targeted therapies (Table 2).

**Table 2.** Expression of biomarkers in type 1 and type 2 endometrial cancer.

| Target     | Function     | Change                        | Type 1, percentage | Type 2, percentage | Outcome                               | Potential targeted therapy                                           |
|------------|--------------|--------------------------------|--------------------|--------------------|---------------------------------------|---------------------------------------------------------------|
| HER-2/ neu | Oncogene     | Enhanced expression           | Rare               | 18–80              | Poor prognosis, aggressive tumor\(^5\) | HER2 inhibitors (afatinib\(^{38}\), trastuzumab\(^{37}\), and lapatinib\(^{56}\)) |
| ER and PR  | Transcription factor | Enhanced expression | 70–73               | 19–24              | Improved overall survival\(^{50}\)     | Tamoxifen, megestrol acetate\(^{46}\), medroxyprogesterone acetate\(^{11}\), letrozole\(^{40,55}\) |
| p53        | Tumor suppressor | Mutation                      | 5–10               | 80–90              | Poor prognosis\(^{42}\)               | Anti-VEGF (bevacizumab\(^{43–46}\)) |
| PIK3CA     | Oncogene     | Mutation                      | 26–90\(^{63}\)     | 26–36              | No association with survival, except exon 9 charge-changing mutations associated with worse survival\(^{57}\) | mTOR inhibitor\(^{68,69}\) (everolimus and temsirolimus\(^{69}\)) ± letrozole\(^{60,51}\) |
| PTEN       | Tumor suppressor | Mutation, deletion, methylation | 35–55             | 0–11               | Poor prognosis\(^{71–73}\)               | mTOR inhibitor\(^{68,69}\) (everolimus\(^{74}\) and temsirolimus\(^{75}\)), evaluating combination with olaparib (ClinicalTrials.gov Identifier: NCT02208375) |
In our practice, we test all primary endometrial cancers with IHC for MMR proteins and, if findings are consistent with Lynch syndrome (absence of staining and no evidence of promoter methylation), proceed to confirmatory testing. In addition, we perform MSI testing if there is a high clinical suspicion for Lynch syndrome even with intact proteins. We perform IHC for HER2/neu status in all serous cancers and confirm overexpression with fluorescence in situ hybridization. We have not yet adapted routine molecular classification; however, we optimistically await further results to guide systemic therapy by molecular class. In the recurrent setting, we recommend molecular profiling, testing for immunotherapy biomarkers (programmed death ligand-1 (PD-L1), MSI, and tumor molecular burden), HER2/neu status in serous cancer, and determining ER and PR status.

**Immunotherapy in endometrial cancer**

Programmed death 1 (PD-1) is an immune checkpoint receptor expressed on tumor-infiltrating T cells that, when activated by PD-L1, blocks T-cell activation and enables immune evasion. About one half of endometrial tumors evaluated in KEYNOTE-028, a phase 1b study, were PD-L1–positive. In this study, investigators evaluated the safety and efficacy of pembrolizumab, an anti–PD-1 monoclonal antibody, in patients with PD-L1–positive tumors. In this heavily pretreated cohort of women, 24 women were enrolled; three patients (13.0%) achieved a partial response and three patients achieved stable disease (median duration of 24.6 weeks). Over half of the patients developed a treatment-related toxicity, of which fatigue, pruritus, pyrexia, and anorexia were the most common. Pembrolizumab was well tolerated overall and resulted in durable response in a subset of patients; however, there remains a need to better identify biomarkers to predict durable response. In 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for all advanced solid tumors that are MSI-high or MMR-D.

Makker et al. recently published an interim analysis of their phase 2 study of pembrolizumab plus lenvatinib in biomarker-unselected advanced endometrial cancer. In the unselected cohort (85% microsatellite stable and 25% PD-L1–positive), 39.6% of patients responded with durable responses (65% had responses greater than 6 months, and median duration of response was not yet achieved). This trial led to FDA breakthrough therapy designation for pembrolizumab with lenvatinib in advanced endometrial cancer. The group has started enrollment for a phase 3 randomized clinical trial of pembrolizumab and lenvatinib versus doxorubicin or paclitaxel. Further research is ongoing to identify a combinatorial approach with other immunotherapies, radiation, or systemic treatment in order to augment the effects of immunotherapy in endometrial cancer.

**Future directions and current clinical trials**

Although there have been great advances in endometrial cancer in the past few years, there remains much left to do as we continue to refine our understanding and treatment of endometrial cancer. Focus will be on better classifying tumors in order to appropriately enroll patients in clinical trials specific to that profile. We need to identify better biomarkers to guide...
personalized therapy as well as to explore combinatorial regimens for targeted therapeutics, hormonal therapy, and immunotherapy. Featured actively recruiting trials include a randomized phase III trial in women with endometrial cancer with high-intermediate risk factors to investigate the role of an integrated clinicopathological and molecular risk profile to guide adjuvant therapy (PORTEC 4-a, ClinicalTrials.gov Identifier: NCT03469674); a phase II trial of paclitaxel, carboplatin, and pembrolizumab in measurable advanced or recurrent endometrial cancer (ClinicalTrials.gov Identifier: NCT02549209); a phase II trial of vaginal cuff brachytherapy followed by adjuvant chemotherpay with carboplatin and dose-dense paclitaxel in patients with high-risk endometrial cancer (ClinicalTrials.gov Identifier: NCT03189446); a phase I study of the Wee I kinase inhibitor AZD1775 in combination with radiotherapy and cisplatin in cervical, upper vaginal, and uterine cancers (ClinicalTrials.gov Identifier: NCT03345784); a randomized phase II study comparing single-agent olaparib, single-agent cediranib, or combination cediranib/olaparib in women with recurrent, persistent, or metastatic endometrial cancer (GY012, ClinicalTrials.gov Identifier: NCT03660826); and multiple trials combining checkpoint inhibitors, immunotherapy, tyrosine kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors, and/or anti-angiogenic inhibitors (TSR042 Garnet study, UC1805, NRG-GY018, AMANDA study, KEYNOTE-077/ECHO-202, KEYNOTE-775, and ROSCAN).

Grant information
The author(s) declared that no grants were involved in supporting this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69(1): 7–34. 
Pubmed Abstract | Publisher Full Text

2. Evans T, Sany O, Pearlman R, et al.: Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. Br J Cancer. 2011; 104(9): 1505–10. 
Pubmed Abstract | Publisher Full Text | Free Full Text

3. Tran AQ, Gehrig P. Recent Advances in Endometrial Cancer. F1000Res. 2017; 6: 81. 
Pubmed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

4. Hogberg T: Adjuvant Chemotherapy in Endometrial Cancer. Int J Gynecol Cancer. 2010; 20(Supp 2): S57–S59. 
Publisher Full Text

5. Rossi EC, Kowalski LD, Scalici J, et al.: A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (Fires trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017; 18(3): 384–92. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

6. Randall ME, Filici VL, Muss H, et al.: Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 2006; 24(1): 36–44. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

7. Abu-Rustum NR, Alekhiar K, Iasonos A, et al.: The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. Gynecol Oncol. 2006; 103(2): 714–8. 
Pubmed Abstract | Publisher Full Text

8. Cardosi RJ, Cox CS, Hoffman MD. Postoperative neuropathies after major pelvic surgery. Obstet Gynecol. 2002; 100(2): 240–4. 
Pubmed Abstract | Publisher Full Text

9. Kang S, Nam JH, Bae DS, et al.: Preoperative assessment of lymph node metastasis in endometrial cancer: A Korean Gynecologic Oncology Group study. Cancer. 2017; 123(2): 263–72. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

10. Hurteau JA: Omitting lymphadenectomy in patients with endometrial cancer. Cancer. 2017; 123(2): 197–9. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

11. Geisbert B, Lörnfero C, Bollino M, et al.: Sentinel lymph node biopsy in endometrial cancer-Feasibility, safety and lymphatic complications. Gynecol Oncol. 2018; 148(3): 491–8. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

12. Bogani G, Ditto A, Leone Reberi Maggiore U, et al.: Sentinel lymph-node mapping in endometrial cancer. Lancet Oncol. 2017; 18(5): e534. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

13. Creasman WT, Morrow CP, Bundy BN, et al.: Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987; 60(8 Suppl): 2036–41. 
Published Abstract

14. Ducie JA, Eriksson AGZ, Ali N, et al.: Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIC endometrial carcinoma at higher risk for nodal disease. Gynecol Oncol. 2017; 147(3): 541–8. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

15. Bogani G, Murgia F, Ditto A, et al.: Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 2019; 153(3): 646–683. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

16. Frumovitz M, Abu-Rustum NR: Tailoring adjuvant treatment in patients with uterine cancer – Authors’ reply. Lancet Oncol. 2018; 19(12): e56. 
Pubmed Abstract | Publisher Full Text

17. Soliman PT, Westin SN, Dioum S, et al.: A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Gynecol Oncol. 2017; 146(2): 234–9. 
Pubmed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

18. Barlin JN, Khtory-Colados F, Kim CH, et al.: The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes. Gynecol Oncol. 2012; 125(3): 531–5. 
Pubmed Abstract | Publisher Full Text

19. Keys HM, Roberts JA, Brunetto VL, et al.: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol. 2004; 92(3): 744–51. 
Pubmed Abstract | Publisher Full Text

20. Mariani A, Webb MJ, Keeney GL, et al.: Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol. 2000; 182(6): 1506–19. 
Pubmed Abstract | Publisher Full Text

21. Mariani A, Dowdy SC, Cliby WA, et al.: Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecol Oncol. 2008; 109: 11–8. 
Pubmed Abstract | Publisher Full Text | Free Full Text

22. Creutzberg CL, van Putten WL, Koper PC, et al.: Surgery and postoperative radiotherapy versus surgery alone for patients with stage 1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000; 356(9231): 1404–11. 
Pubmed Abstract

23. Creutzberg CL, Nout RA, Lybeer MLM, et al.: Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011; 81(4): e631–4. 
Pubmed Abstract | Publisher Full Text

24. Randall ME, Filici V, Meckeen DS, et al.: Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. J Clin Oncol. 2019; JCO1801575. 
Pubmed Abstract | Publisher Full Text | F1000 Recommendation

25. Matei D, Filici VL, Randall M, et al.: A randomized phase III trial of cisplatin
and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. J Clin Oncol. 2017; 35: 5505. Publisher Full Text

26. de Boer SM, Powell WE, Mileshkin L, et al.: Adjuvant chemoradiation therapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018; 19(3): 295–309. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

27. Nout RA, Smitt V, Putter H, et al.: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010; 375(9727): 816–23. PubMed Abstract | Publisher Full Text | F1000 Recommendation

28. Greven K, Winter K, Underhill K, et al.: Final analysis of RT0G 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy for surgery for patients with high-risk endometrial cancer. Gynecol Oncol 2006; 103(1): 155–9. PubMed Abstract | Publisher Full Text

29. Wu-Jin KM, Abu-Rustum NM, Bradley KM. National Comprehensive Cancer Network, Uterine Neoplasms (Version 1.2019). Accessed November 22, 2018 Reference Source

30. Hamilton CA, Cheung MK, Osann K, et al.: Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006; 94(5): 642–6. PubMed Abstract | Publisher Full Text | Free Full Text

31. Zhao S, Choi M, Overton JD, et al.: Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. Proc Natl Acad Sci U SA. 2013; 110(8): 2916–21. PubMed Abstract | Publisher Full Text | Free Full Text

32. Buytjoorova TN, Brenner CA, Singh M: Endometrioid carcinomas: is there a survival difference? Pathology. 2003; 35(3): 211–7. PubMed Abstract | Publisher Full Text

33. del Carmen MG, Birrer M, Schorge JO: Cancer Genome Atlas Research Network. Kandoth C, Schultz N, et al.: Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497(7447): 67–73. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

34. Talhouk A, McConney MK, Leung S, et al.: A clinically applicable molecular-based classifier for endometrial cancers. Br J Cancer. 2015; 113(2): 299–310. PubMed Abstract | Publisher Full Text | Free Full Text

35. Cosgrove CM, Titchler DL, Coom DE, et al.: An NRG Oncology/GOG study of molecular classification for risk prediction in endometrioid endometrial cancer. Gynecol Oncol. 2018; 148(1): 174–80. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

36. Talhouk A, McConney MK, Leung S, et al.: Confirmation of ProfMiaE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017; 123(5): 802–13. PubMed Abstract | Publisher Full Text | F1000 Recommendation

37. de Grèvre J, Teugels E, Geers C, et al.: Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/new. Lung Cancer. 2012; 76(1): 123–7. PubMed Abstract | Publisher Full Text

38. Geyer CE, Forster J, Lindquist D, et al.: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006; 355(26): 2733–43. PubMed Abstract | Publisher Full Text | F1000 Recommendation

39. Chambers JT, MacDonald S, Eisenfield A, et al.: Phase II study of axitinib as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2006; 103(2): 523–6. PubMed Abstract | Publisher Full Text

40. Moore DH, Blessing JA, Dunton C, et al.: Dactinomycin in the treatment of recurrent or persistent endometrial carcinoma: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 1999; 75(3): 473–5. PubMed Abstract | Publisher Full Text

41. Homesley HD, Blessing JA, Sorsky J, et al.: Phase II trial of liposomal doxorubicin at 40 mg/m2 every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2005; 98(2): 294–8. PubMed Abstract | Publisher Full Text

42. Plaxe SC, Blessing JA, Husseinbadeh N, et al.: Phase II trial of paclitaxel and carboplatin in patients with persistent or recurrent endometrial carcinoma: A Gynecologic Oncology Group Study. Gynecol Oncol. 2002; 84(2): 241–4. PubMed Abstract | Publisher Full Text

43. Miller DS, Blessing JA, Lentz SS, et al.: A phase II trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2002; 87(3): 247–51. PubMed Abstract | Publisher Full Text

44. Fracasso PM, Blessing JA, Molpus KL, et al.: Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2006; 103(2): 523–6. PubMed Abstract | Publisher Full Text

45. Schilder RJ, Blessing JA, Pearl ML, et al.: Evaluation of irinotecan (CPT-11) in the treatment of recurrent or persistent endometrial carcinoma: A Phase II study of the Gynecologic Oncology Group. Invest New Drugs. 2004; 22(3): 343–9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

46. Grenady EC Jr, Blessing JA, Burger R, et al.: A phase II trial of flavopiridol as second-line chemotherapy of endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2005; 98(3): 249–53. PubMed Abstract | Publisher Full Text

47. Aghajanian C, Sill MW, Darcy KM, et al.: Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011; 29(16): 2259–65. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

48. Slimovitz BM, Jiang Y, Yates MS, et al.: Phase II study of everolimus and letrozole in patients with recurrent endometrial cancer. J Clin Oncol. 2015; 33(8): 930–6. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

49. Bassist J, Campone M, Piccart M, et al.: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012; 366(6): 520–9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

50. Howitt BE, Shukla SA, Shol LM, et al.: Association of Polyomavirus e-Mutated and Microsatellite-Instable Endometrial Cancers With Neutonigant Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol. 2015; 1(9): 1319–23. PubMed Abstract | Publisher Full Text

51. Talhouk A, McConney MK, Leung S, et al.: A clinically applicable molecular-based classifier for endometrial cancers. Br J Cancer. 2015; 113(2): 299–310. PubMed Abstract | Publisher Full Text | Free Full Text

52. Gounder MM, Taylor AM, Neve RL, et al.: Identification of specific genetic alterations that correlate with response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics. Mol Cancer Ther. 2016; 15(10): 2475–83. PubMed Abstract | Publisher Full Text

53. Wheler JJ, Janku F, Naing A, et al.: TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics. Mol Cancer Ther. 2016; 15(10): 2475–83. PubMed Abstract | Publisher Full Text
65. Schweenerté M, Lazar V, Validere P, et al.: VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy. Cancer Res. 2015; 75(7): 1187–90. PubMed Abstract | Publisher Full Text

66. Moir A, Filcat VL, Levine DA, et al.: Evidence for synthetic lethality between bevacizumab and chemotherapy in advanced p53 null endometrial cancers. Oral presentation at: 2018 Society of Gynecologic Oncology Annual Meeting on Women’s Cancer: March 24–27, New Orleans, LA. 2018.

67. Mjos S, Werner HM, Birkeland E, et al.: PIK3CA exon9 mutations associate with reduced survival, and are highly concordant primary tumors and metastases in endometrial cancer. Sci Rep. 2017; 7(1): 10240. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

68. Janku F, Wheeler JJ, Westin SN, et al.: PIK3CAAKTmTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol. 2012; 30(8): 777–82. PubMed Abstract | Publisher Full Text | Free Full Text

69. Janku F, Hong DS, Fu S, et al.: Assessing PIK3CA and PTEN in early-phase trials with PIK3CAKTmTOR inhibitors. Cell Rep. 2014; 6(2): 377–87. PubMed Abstract | Publisher Full Text | Free Full Text

70. Oza AM, Elit L, Tsao MS, et al.: Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. J Clin Oncol. 2011; 29(24): 3278–85. PubMed Abstract | Publisher Full Text | Free Full Text

71. Athensiadou P, Athanassiades P, Grapsa D, et al.: The prognostic value of PTEN, p53, and beta-catenin in endometrial carcinoma: a prospective immunohistochemical study. Int J Gynecol Cancer. 2007; 17(5): 697–704. PubMed Abstract

72. Terakawa N, Kanamori Y, Yoshida S: Loss of PTEN expression followed by Akt phosphorylation is a poor prognostic factor for patients with endometrial cancer. Endocr Relat Cancer. 2003; 10(2): 193–8. PubMed Abstract | Publisher Full Text | Free Full Text

73. Salvesen HB, MacDonald N, Ryan A, et al.: PTEN methylation is associated with advanced stage and microsatellite instability in endometrial carcinoma. Int J Cancer. 2001; 91(1): 22–6. PubMed Abstract | Publisher Full Text | Free Full Text

74. Slomovitz BM, Lu KH, Johnston T, et al.: A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. Cancer. 2010; 116(23): 5415–9. PubMed Abstract | Publisher Full Text | Free Full Text

75. Bachmann IM, Halvorsen OJ, Collett K, et al.: EZH2 expression is associated with high proliferation and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. J Clin Oncol. 2006; 24(2): 268–73. PubMed Abstract | Publisher Full Text | Free Full Text

76. Mizouchi H, Nasim S, Kudo R, et al.: Clinical implications of K-ras mutations in malignant epithelial tumors of the endometrium. Cancer Res. 1992; 52(10): 2777–81. PubMed Abstract

77. Falchook GS, Lewis KD, Infante JR, et al.: Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol. 2012; 13(8): 782–9. PubMed Abstract | Publisher Full Text | Free Full Text

78. Cox AD, Fesk SW, Kimmelman AC, et al.: Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 2014; 13(11): 828–51. PubMed Abstract | Publisher Full Text | Free Full Text

79. Zighelboim I, Goodfellow PJ, Gao F, et al.: Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. J Clin Oncol. 2007; 25(15): 2042–8. PubMed Abstract | Publisher Full Text

80. Piuoters JM, Matias-Guiu X: Immunotherapy in Endometrial Cancer: In the Nick of Time. Clin Cancer Res. 2016; 22(23): 6523–5. PubMed Abstract | Publisher Full Text

81. Hampel H, Frankel W, Panescu J, et al.: Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res. 2006; 66(15): 7810–7. PubMed Abstract | Publisher Full Text

82. Mo Z, Liu J, Zhang Q, et al.: Expression of PD-1, PD-L1 and PD-L2 is associated with differentiation status and histological type of endometrial cancer. Oncl Lett. 2012; 6(2): 944–50. PubMed Abstract | Publisher Full Text | Free Full Text

83. Vanderstraeten A, Luyten C, Verbist G, et al.: Mapping the immunosuppressive environment in uterine tumors: Implications for immunotherapy. Cancer Immunol Immunother. 2014; 63(6): 545–57. PubMed Abstract | Publisher Full Text | Free Full Text

84. Ott PA, Bang YJ, Berton-Rigaud D, et al.: Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1-Positive Endometrial Cancer: Results From the KEYNOTE-028 Study. J Clin Oncol. 2017; 35(22): 2535–41. PubMed Abstract | Publisher Full Text | Free Full Text

85. Landsmeer S, Smit JH, Waterreus AM, et al.: Utility of Genomic Analysis In Circulating Tumor DNA from Patients with Carcinoma of Unknown Primary. Cancer Res. 2017; 77(10): 2428–36. PubMed Abstract | Publisher Full Text | Free Full Text

86. Kato S, Krishnamurthy N, Banks KC, et al.: Immune Checkpoint Inhibition in Gynecologic Malignancies: An Evidence-Based Systematic Review. Front Immunol. 2018; 9: 1552. PubMed Abstract | Publisher Full Text | Free Full Text

87. Longoria TC, Eskander RN: Immunotherapy in endometrial cancer - an evolving therapeutic paradigm. Gynecol Oncol Res Pract. 2015; 2: 11. PubMed Abstract | Publisher Full Text | Free Full Text

88. Pardoll DM: The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12(4): 252–64. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

89. Ishida M, Takeya M, Takeya M, et al.: Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002; 99(19): 12293–7. PubMed Abstract | Publisher Full Text | Free Full Text

90. Makker V, Racas D, Vogeizang NJ, et al.: Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019; 20(5): 711–8. PubMed Abstract | Publisher Full Text | F1000 Recommendation
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Version 1

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Competing Interests: Anil K Sood is a consultant for Merck and Kiyatec, receives research funding from M-Trap, and is a stock holder in Biopath.

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Competing Interests: No competing interests were disclosed.

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