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Review Article

Endometrial cancer: Molecular markers and management of advanced stage disease

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HIGHLIGHTS

- Controversy exists regarding the role of radiation in the management of advanced stage endometrial cancer.
- Immunotherapy and novel treatments that target molecular defects show promise in the treatment of endometrial cancer.
- Understanding how and when to test the tumor for molecular markers and how to use the findings remain a challenge.
- Personalized treatments and the use of new biologics have shown promise in the pre-clinical and clinical settings.
- Additional trials are needed to understand how to combine targeted therapies with other therapies to maximize response.

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ABSTRACT

Endometrial cancer is the most prevalent gynecologic cancer in the United States. Over the last 10 years, death rates from endometrial cancer have been rising about 1.4% per year. Traditionally endometrial cancer treatment has been driven by stage and histology. Recent studies have, however, shown that cancers of the same stage and histology have very distinct molecular and genomic profiles. Translational research is progressing rapidly and endometrial cancer-specific precision medicine is evolving. The first tissue agnostic therapy based on the molecular profile of the tumor was approved by the FDA this year. The approval of immune checkpoint inhibitor, pembrolizumab (anti-PD-1), for all solid tumors with defective DNA mismatch repair, could benefit 20–30% of patients with advanced endometrial cancer. Other genomic changes and molecular markers in endometrial cancer, such as hormone receptor status, could lead to more tailored therapy in the future. Pre-clinical and clinical investigations of targeted therapies suggest efficacy for some agents. Single agent targeted therapies, however, have modest activity. Identifying biomarkers that effectively determine response to targeted therapy remains a challenge. The next generation of clinical trials will focus on novel combinations and how to best utilize the advances that have been made in sequencing technology and bioinformatics. Although there is currently an immense body of data and many options for obtaining genomic characteristics of endometrial cancer, how to interpret and utilize this data is still being explored. This review will summarize the important trials that have led to the treatment options we have for advanced and/or recurrent endometrial cancer and discuss the important studies that have led to a better understanding of the distinctive molecular and genomic profiles within endometrial cancer. We will review the current status of biomarker-driven targeted therapy in endometrial cancer and the rationale behind ongoing clinical trials that are utilizing novel targeted agents.

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1. Introduction

Endometrial cancer will affect 61,380 women in the United States in 2017 and will result in 10,920 deaths with similar incidence and mortality rates world-wide [1]. Frequently, outcomes for adenocarcinoma of the endometrium are favorable because of the early symptoms of irregular/postmenopausal vaginal bleeding that trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate [2,3]. This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. For women who present with advanced stage or recurrent disease that is not amenable to localized therapies, outcomes are poor. Controversies exist about the role of radiation in advanced stage disease. After initial therapy, there are limited treatment options, with no standard options available at the time of subsequent recurrence or progression. To further improve outcomes for endometrial cancer patients overall, better approaches to identify high-risk patients to tailor treatment are needed to provide the best long-term survival.

Molecular characterization of endometrial cancer is advancing rapidly, and understanding how specific mutations or combinations of molecular features can lend themselves to targeted therapeutics is paramount in the treatment of advanced or recurrent endometrial cancer. Multiples studies, including the landmark Cancer Genome Atlas Project (TCGA) for endometrial cancer, have revealed common endometrial cancer mutations and features that are highly characteristic of uterine epithelial malignancies [4]. Findings from several of these studies will be highlighted in this review [4–15].

1.1. Staging and NCCN treatment guidelines

High-risk endometrial cancer usually refers to either stage III/IV endometrioid histology or high-risk histology (UPSC, clear cell, carcinosarcoma). In 2009, several changes in the staging of endometrial cancer were made to better reflect outcomes associated with stage. Specifically, in advanced stage disease, stage IIIC was subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes. For stage IIIA to IIIC disease, the National Comprehensive Cancer Network (NCCN)-recommended treatment options are systemic therapy and/or external beam radiotherapy (EBRT) with or without vaginal brachytherapy (Fig. 1A). For stage IVA/IVB disease that is debulked with no gross residual disease or microscopic abdominal disease, systemic therapy remains the mainstay of treatment and can be combined with EBRT and/or vaginal brachytherapy (Fig. 1A). For high-risk tumor histologies at stage 1B or higher, the NCCN treatment recommendation is for chemotherapy with or without either EBRT or vaginal brachytherapy (Fig. 1B). Table 1 summarizes the NCCN recommendations for systemic therapy for recurrent, metastatic, or high-risk disease. It is important to note that the NCCN strongly encourages all of these patients (recurrent, metastatic or high risk) to participate in clinical trials. The landmark trials that led to the NCCN recommendations are summarized below.

2. Summary of landmark clinical trials

2.1. Role of radiation

The role of radiation in advanced stage endometrial cancer remains an on-going debate. Key areas of uncertainty include: 1) Which patients should have radiation—all or select subsets?, 2) When should it be used? Before, during, or after chemotherapy?, and 3) What sort of radiation therapy—EBRT or brachytherapy?

Advanced stage patients receiving radiation alone are generally treated with extended field radiation after surgery. Survival rates for this group are modest (30–40%) with clear indication that surgical procedures and a range of other clinicopathologic features impact outcomes. Mariani et al. reported on 122 patients with node-positive disease. At 5 years, risk of pelvic recurrence in patients with inadequate lymph node (LN) dissection and/or no radiotherapy (RT) compared to patients with adequate LN dissection and RT was 57% and 10% respectively [16]. A study by Greven et al., reported 105 irradiated patients with stage IIIC had a pelvic failure rate of 21% [17]. Similarly, Mundt and colleagues described two series with 30 stage IIIC patients treated with irradiation after surgery that had an infield failure rate of 23%

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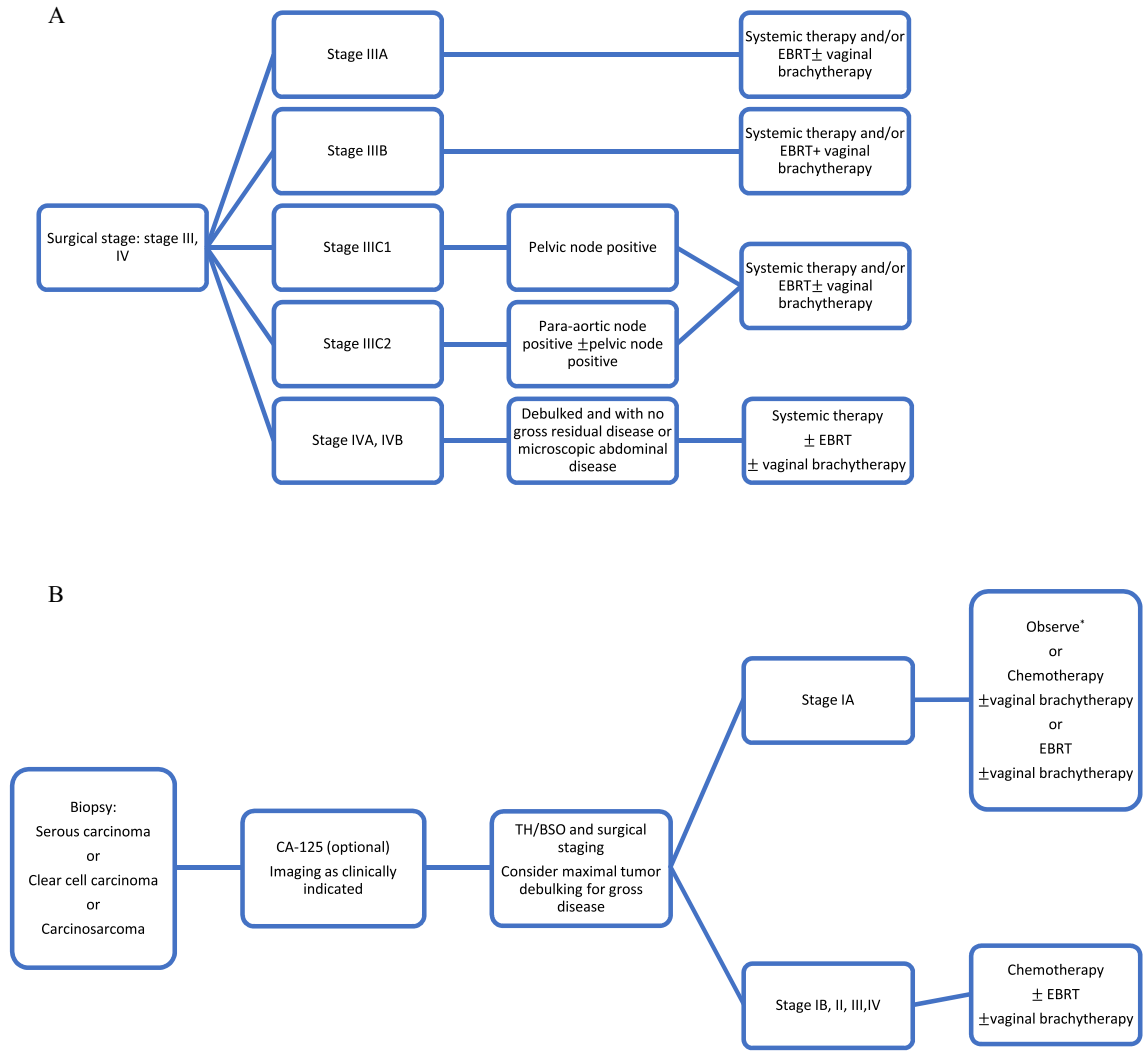

Fig. 1. NCCN-recommended treatment options. Fig 1A. Treatment options for stage IIIA-IVB. 1B. Diagnosis and treatment for IA tumors and IB and higher tumors.

[18]. A significant number of stage III patients fail in the abdomen, prompting investigators to evaluate abdominal RT in clinical trials.

Landmark trials that have investigated the role of radiation are summarized in Table 2. In GOG 122, a phase III trial, 396 stage III/IV optimally debulked patients were randomized to whole abdomen radiation versus 7 cycles of combined doxorubicin/Adriamycin (A) and cisplatin (P) treatment, with an additional cycle of cisplatin. This GOG trial reported that AP chemotherapy improved progression-free survival (PFS) and overall survival (OS) when compared with whole abdominopelvic RT; however, acute toxicity (e.g., peripheral neuropathy) was greater in the AP chemotherapy arm and the pelvic recurrence rate was lower in the RT group [19]. Another trial that included stage I to III patients compared RT vs AP + cyclophosphamide (CP); it showed no difference between the two arms [20]. Another single arm trial included 44 stage I-III patients treated with RT and intravaginal brachytherapy given concurrently with cisplatin on day 1 and 28 of radiation, followed by 4 cycles of cisplatin and paclitaxel showed a 4 year disease-free survival (DFS) of 72% and OS of 77% for stage III patients [21]. The OS in this trial was 85% at 4 years—considerably better than the 5 year OS (66%) in the chemotherapy arm of the previous trial reported by Maggi et al. [20,21] In GOG 184, (the follow up study for GOG 122) 552 patients with stage III-IV disease were randomized to either tumor volume directed irradiation + AP or AP + paclitaxel (TAP), and the PFS was equivalent in both arms [22]. Two recent trials comparing either the combination of chemotherapy and radiation to radiation alone (Post-Operative Radiation Therapy in Endometrial Cancer 3 [PORTEC-3]) or to chemotherapy alone (GOG 258) were presented at ASCO in June 2017 [23,24]. PORTEC-3 included patients with stage I grade 3 disease with deep myometrial invasion, stage II or stage III, and clear cell or papillary serous histology. Patients were randomized to pelvic radiation alone or

Table 1
NCCN chemotherapy recommendations for recurrent, metastatic, or high-risk endometrial cancer.

Single agent	Multi-agent chemotherapy regimens preferred if tolerated
Cisplatin	Carboplatin/paclitaxel
Carboplatin	Cisplatin/doxorubicin
Doxorubicin	Cisplatin/doxorubicin/paclitaxel
Liposomal doxorubicin	Carboplatin/docetaxel
Paclitaxel	
Topotecan	
Bevacizumab	
Temsirolimus	
Docetaxel	
Ifosfamide	

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Table 2
Landmark clinical trials using radiation.

Study	Population (stage)	n	Regimen	Results
Randall, ME, et al., 2006 [19]	III–IV	396	WART A (60 mg/m2) P (50 mg/m2) × 7 + 1 cycle of P only	PFS (5 years): 42% (AP) vs. 38% (WART) (HR 0.71) OS (5 years): 53% (AP) vs. 42% (WART) (HR 0.68)
Maggi, R., et al., 2006 [20]	IC, II, III	345	EBRT vs AP + cyclophosphamide	PFS (5 years): 63%(RT) vs 63% (CT) OS (5 years): 69%(RT) vs 66% (CT)
Kuoppala, T., et al., 2008 [104]	IA–B, G3 IC–IIIA	156	RT + P + cyclophosphamide + epirubicin vs. RT only	OS (5 years): NS (84.7% (RT) vs. 82.1% (RT + CT))
Susumu, N., et al., 2008 [105]	IIA–III	385	RT vs CT (AP + cyclophosphamide)	PFS (5 years): 83.5% (RT) vs 81.8% (CT) OS (5 year): 85.3% (RT) vs 86.7% (CT)
Homesley, HD, et al., 2009 [22]	III–IVA	552	EBRT + A + P ± T	RFS (3 years): 62% (AP) vs 59% (APT)
Hogberg, T., et al., 2010 [106]	I–III	534	RT vs RT + CT after surgery	PFS (5 years): HR 0.63, $p = 0.009$ OS (5 year): HR 0.69, $p = 0.07$
De Boer, SM, et al., 2017 [107]	I–III	660	RT + PTC vs RT	FFS (5 years): 75.5% (CTRT) vs 68.9% (RT) HR 0.77 (NS) OS (5 year): 81.8%(CTRT) vs 76.7%(RT) HR 0.79 (NS)
Matei, D., et al., 2017 [24]	III–IV	813	P + RT → TC vs TC	*No overall improvement in recurrent-free survival*

A = Adriamycin/doxorubicin, P = cisplatin, T = paclitaxel, WART = whole abdomen radiotherapy, RT = radiation, CT = chemotherapy, C = carboplatin, EBRT = external beam radiotherapy, PFS = progression free survival, OS = overall survival, RFS = recurrence free survival, FFS = failure free survival, NS = not significant, HR = hazard ratio.

two cycles of cisplatin chemotherapy delivered during radiation followed by 4 cycles of carboplatin and paclitaxel. The combination arm had a better OS, but it was not statistically significant; however, the 5-year failure-free survival was 75.5% (combination) versus 68.6% (radiotherapy alone) with a hazard ratio of 0.71 ($p = 0.22$). In addition, the 5-year failure-free survival among the 46% of patients with stage III disease was statistically significant with a hazard ratio of 0.62 in favor of the combination therapy [23]. In GOG 258, women with stage III and IV endometrial cancer who had no/minimal residual disease (<2 cm) after surgery were randomized to volume directed postoperative irradiation with concurrent cisplatin followed by 4 cycles of carboplatin/paclitaxel or 6 cycles carboplatin/paclitaxel alone. There was no difference in recurrence-free survival; however, the chemo + radiation arm had fewer vaginal and pelvic/periaortic recurrences, but more distant recurrences. The overall survival data for GOG 258 are not mature yet [24].

2.2. First line chemotherapy

There have been several important randomized studies performed addressing the issue of optimal chemotherapy for patients with high-risk endometrial cancer (Table 3). These studies have focused on three active agents identified in phase II trials: doxorubicin/Adriamycin (A), platinum agents (P), and paclitaxel (T). GOG 107 established the superiority of combination A and P over single agent A by virtue of superior response rate (RR) and PFS, although no difference in OS was observed [25]. GOG 177 evaluated the addition of T to AP (TAP) and found that TAP was superior to AP in terms of RR, median PFS and OS [26]. In GOG 209, TAP was compared to T and carboplatin (TC) in a non-inferiority trial. This study (presented only in abstract form) found that TC was not inferior to TAP and had less toxicity. Based in large part on the GOG 209 trial, TC has become the current standard of care [27]. Hormonal therapies (medroxyprogesterone acetate, megestrol acetate and tamoxifen), when given to chemotherapy-naïve patients, can result in response rates of up to 33%, but responses are of short duration (median PFS of approximately 3 months) [28–32].

2.3. Recurrent endometrial cancer

The GOG-129 series (all single arm trials) has evaluated cytotoxic agents in patients with one prior cytotoxic regimen and has tested and published on 13 different agents. Finding for most of the studies have been published (Table 4), with only one agent meeting the 15% response rate bar for further accrual [33–45]. GOG-129C evaluated paclitaxel and reported a response rate of 25%. The GOG-129C trial took place in an era before paclitaxel was used as upfront therapy, and thus the high (25%) response rate seen is not expected at this time when primary treatment frequently includes paclitaxel. A large, international randomized phase III trial of ixabepilone versus physicians' choice of paclitaxel or doxorubicin found no benefit with ixapebilone and a median PFS in the control arm of 4.0 months and median OS of 12.3 months [46]. There have been 10 published phase II trials (GOG-229 series) exploring targeted agents in the setting of recurrent disease following primary chemotherapy targeting the epidermal growth factor receptor (GOG 229D and 229C), MEK1/2 pathway (GOG 229H) and angiogenesis

Table 3
Historic randomized (two-arm) clinical trials with systemic chemotherapy.

Author/year	Population	n	Regimen	Results
van Wijk, FH, et al., 2003 [108]	Stage III–IV or recurrent	177	A (60 mg/m^2) vs AP(60 mg/m^2/50 mg/m^2) every 4wk	RR: 17% vs 43% OS: 7 vs 9
Thigpen, JT, et al., 2004 [25]	Stage III/IV or recurrent	281	AP (60 mg/m^2/50 mg/m^2) vs. A (60 mg/m2) every 3 weeks	RR: 25% vs 42% PFS: 3.8 vs 5.7 m (HR 0.73) OS: 9 vs 9.2 m
Fleming, GF, et al., 2004 [26]	Stage III–IV or recurrent	240	AP (60 mg/m2/50 mg/m^2) vs TAP (45 mg/m^2/50 mg/m^2/160 mg/m^2)	RR: 57% vs 34% PFS: 8.3 vs 5.3 m OS: 15.3 vs 12.3 m
Miller, D., et al., 2012 [27]	Stage III–IV or recurrent	1312	TAP (45 mg/m^2/50 mg/m^2/160 mg/m^2) vs T + C (175 mg/m^2/AUC 6)	T + C not inferior

A = Adriamycin/doxorubicin, D = doxorubicin, P = cisplatin, T = paclitaxel, C = carboplatin, PFS = progression free survival, OS = overall survival, RFS = recurrence free survival, RR = recurrence risk.

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Table 4
GOG 129 series evaluating cytotoxic agents (Phase II single arm trials, all recurrent Endometrial Cancer).

Author/Year	n	Regimen	Results
Rose, PG, et al., 1996 [43]	99	Etoposide 50 mg/m2 (30 mg/m2 for prior RT) for 21 d, q28 d	"Platinum-resistant" RR: 26.8% OS: 10.8 m "Platinum-sensitive" RR: 34.1% OS: 16.5 m
Moore, DH, et al.,1999 [40]	27	Dactinomycin 2 mg/m^2 IV q4 wks	CR: 1 PR: 2 ORR: 12%
Muggia, FM, et al., 2002 [41]	46	Pegylated liposomal doxorubicin (PLD) IV 50 mg/m2 q4 wks	RR: 9.5% OS: 8.2 months
Plaxe, S., et al., 2002 [42]	28	Initil 750 mg/m^2 IV q3 wks	PR: 1 CR: 0
Miller, DS, et al., 2002 [39]	29	Topotecan 0.5 to 1.5 mg/m^2 IV for 5 d, q3 wks	performance status (PS) of 0, 1: 41% PS of 1: 50% PS of 2: 9%
Lincoln, S., et al., 2003 [37]	50	Paclitaxel 200 mg/m^2 q21 d or 175 mg/m^2	RR: 27.3% OS: 10.3 months
Schilder, R., et al., 2004 [44]	25	Irofulven 11 mg/m^2 IV for 4 d q28 d	CR: 4% SD: 28% with duration of 10.4 m
Grendys, E., et al., 2005 [36]	26	Flavopiridol 50 mg/m^2 IV d1, 2, 3, q21 d	No response
Fracasso, PM, et al., 2006 [34]	54	Oxaliplatin 130 mg/m^2 IV q21 d	ORR: 13.5% CR: 5.8% PR: 7.7
Garcia, A., et al., 2008 [35]	27	Docetaxel 36 mg/m^2 d 1, 8 and 15, q28 d	PR: 7.7% SD: 30.8% PD: 53.8%
Miller, DS, et al., 2009 [38]	27	Pemetrexed 900 mg/m^2 IV q21 d	PR: 4% SD: 44% PD: 44% PFS: 2.7 months
Dizon, DS, et al., 2009 [33]	52	Ixabepilone 40 mg/m^2 IV d 1 of a 21-d cycle	ORR: 12% PFS: 2.9 months 6 m PFS: 20%
Tait, DL, et al., 2011 [45]	24	Gemcitabine 800 mg/m^2 on d 1 and 8 q21 d	PR: 4% SD: 39% PD: 52% PFS: 1.7 months

PFS = progression free survival, OS = overall survival, RFS = recurrence free survival, RR = recurrence risk, PR = partial response, SD = stable disease, PD = progressive disease, ORR = overall response rate, CR = complete response, q = every, d = days, m = months, wks = weeks.

pathways [47–57]. Of these single agent studies, only bevacizumab, aflibercept and brivanib demonstrated therapeutic activity warranting further investigation [50,52,56].

3. Molecular features of endometrial cancer

3.1. Type I vs. Type II endometrial cancer

Historically, endometrial cancer has been classified into two types: Type I and Type II [58]. These two groups have distinct clinicopathologic features and, not surprisingly, have mutational profiles that differ significantly. Type I tumors are primarily the endometrioid histologic subtype, and the non-endometriod histology fall under the Type II category. Differences in the molecular changes that characterize Type I and Type II have been reported and reviewed extensively. *PTEN* loss is found in about 83% of Type I tumors, whereas it is only found in 11% of Type II tumors. In contrast, *TP53* mutations are found in 90% of Type II tumors and only 10–20% of Type I tumors [59]. *PIK3CA* mutations are more frequently seen in Type I tumors (20–40%) than Type II tumors (20%), but *PIK3CA* amplifications are more common in Type II tumors (almost 50%) compared to Type I (<15%). *PIK3R1* mutations are also more common in Type I tumors (43% vs. 12%).

3.2. Molecular classification of endometrial cancer

Potentially more important than Type I vs. II classification is the newer grouping of endometrial cancer based on the TCGA categorization into four distinct classes: 1) DNA polymerase epsilon (*POLE*) ultramutated (very high mutation rates); 2) microsatellite instability (MSI) hypermutated, most frequently associated with *MLH1* promoter methylation; 3) copy-number low, endometrioid tumors characterized by high frequency of *CTNNB1* mutations and a range of other modest to highly recurrent gene defects; and 4) copy-number high, characterized by *TP53* mutation and high frequency of *FBXW7* and *PPP2R1A* mutations. Overall, endometrial tumors have few copy number alterations and infrequent *TP53* mutation, whereas *PTEN, CTNNB1, PIK3CA, ARID1A*, *KRAS* and mutations in members of the SWI/SNF chromatin remodeling complex are relatively frequent [7]. Piulats et al. used a cohort of 50 patients with high grade endometriod adenocarcinoma to show the differences in clinical outcomes among the subgroups. At 48 months, cancer specific survival/disease-specific survival was 100% in the *POLE*-mutant group, 82% in the MSI group, 77.8% in the copy-number low group and 42.9% in the copy-number high group. These data show that survival is greatest among the *POLE*-mutant group. The *p*-value for this analysis was 0.065; although not statistically significant, the data indicates that molecular classification holds prognostic significance in these patients [60]. Stelloo et al. also looked at clinical outcomes among the molecular subgroups. They found a five-year recurrence-free survivial of 93% for group 1 (*POLE*-mutant) and 95% for group 2 (microsatellite instability) versus 52% for group 3 (copy-number low) and 42% for group 4 (p53-mutant) [14]. A study by Talhouk et al. used the p53 wild-type subgroup (copy-number low TCGA classification) as a reference to look at OS and RFS among the subgroups. For OS, microsatellite instable, *POLE*-mutant and p53-mutant subgruops has hazard ratios of 1.80, 0.23 and 3.29, respectively.

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Recurrence-free survival hazard ratios for the same three subgroups were 0.85, 0.16 and 2.19 [61]. A pragmatic molecular classification tool, ProMisE, has been developed, confirmed and validated to provide consistent categorization of tumors. It identifies the four distinct prognostic molecular subtypes based on the TCGA categorization. [62]. Talhouk et al. used ProMisE to show OS and PFS differences between the subgroups. In comparison to the p53 wild-type subgroup (copy-number low TCGA classification), microsatellite instable, *POLE*-mutant and p53-mutant had overall survival hazard ratios of 2.21, 0.78 and 3.54, respectively. PFS hazard ratios were 3.30, 0.51 and 7.84. Their findings once again highlight the association of the subgroups to clinical outcomes [63]. Studies are ongoing to determine how tumor molecular features and individual markers are associated with tumor prognosis and potential response to targeted therapy. Prospective clinical trials that include integrated and integral biomarkers are needed to better understand the relationships between molecular states and patient outcomes. PORTEC-4a, which is a randomized trial investigating standard versus molecular profile-based recommendation for radiotherapy after surgery for women with early stage endometrial cancer, is on-going. Additional studies in advanced stage endometrial cancer are also needed.

3.3. Mismatch repair deficiency

Mismatch repair is essential to the maintenance of genomic stability, primarily through the repair of base substitution mismatches and small insertion deletion mutations. Loss of mismatch repair results in a tumor mutator phenotype. Failure to repair strand-slippage mutations that occur naturally during DNA synthesis leads to microsatellite instability (MSI). MSI is an easily identified molecular phenotype. Up to 30% of endometrial cancers show MSI. Mutations in the *MLH1*, *MSH2*, *MSH6* and *PMS2* genes can result in loss of MMR. A small subset of MSI tumors are in women with Lynch Syndrome (discussed further in the next section) [64]. The primary cause of MMR deficiency in endometrial cancer is due to an epigenetic defect: hypermethylation of *MLHI* promoter. Some cancers do have somatic mutations of MMR genes. Mutations accumulate at a high rate as a result of mismatch repair deficiency. One example is of a gene frequently mutated in MSI-positive endometrial cancers, *MRE11*, which is a double strand break repair gene. Identifying patients with endometrial cancers with defective DNA mismatch, as well as those with impaired DSB, will allow us to better identify which patients will be more likely to respond to treatments that target those defects. Immunotherapies, such as immune checkpoint inhibitors (anti-programmed death [PD]-1 and anti-PD-ligand 1 antibodies) are effective in tumors with MSI [65]. The FDA granted accelearted approval to pembrolizumab (anti-PD-1) for adult and pediatric patient with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficiet (dMMR) solid tumors that have progressed following prior treatment on May 23, 2017. This was the FDA's first tissue site agnostic approval. The approval was based on a pooled analysis of five trials, which showed objective response rate (ORR) of 39.6% that lasted six months or more in 78% of these patients. In the KEYNOTE-028 trial, which was a phase Ib multicohort trial evaluating the safety and efficacy of pembrolizumab in patients with PD-L1 positive advanced solid tumors, antitumor activity and a favorable safety profile was demonstrated in patients with heavily pretreated advanced endometrial cancer [66,67]. Many other studies investigating immunotherapies as effective treatments in tumors with MSI are ongoing [68]. Another immune modulatory molecule, indoleamine 2,3-dioxygenase (IDO), has been shown to be prevalent in endometrial carcinoma and mismatch repair-deficient cancers were more likely to be >25% IDO-positive. Furthermore, the majority of PD-L1 positive cancers were shown to express IDO, suggesting that combination therapy with anti-IDO and anti-PD1/PD-L1 may be beneficial in these tumors [69].

3.4. Germline/inherited mutations in DNA mismatch repair

Although most endometrial cancer is caused by sporadic mutations, inherited mutations account for 3–5% of endometrial cancers, the majority of which have Lynch syndrome. Endometrial cancer is the most common extra-colonic malignancy associated with Lynch syndrome, with a lifetime risk of 40–60% in these women [70]. The genetics of Lynch syndrome and implications for endometrial cancer patients and their relatives has been reviewed extensively [71–74] The tumor MSI that is characteristic of Lynch syndrome endometrial cancers affords opportunities for molecularly guided immune check-point blockade therapy.

4. Select endometrial cancer biomarkers

4.1. PTEN and PI3K/AKT/mTOR pathway

Molecular biomarkers can be diagnostic, prognostic and/or predictive of response to a certain therapy. Numerous biologic and combined biologic/cytotoxic therapies that target the PI3K pathway have been explored. Up to 90% of endometrioid endometrial cancers lack *PTEN* expression, making this the most commonly altered pathway in endometrial cancer [75]. PTEN is a key regulator of the PI3K pathway, ultimately impacting mammalian target of rapamycin (mTOR) activity through a signaling cascade. The phosphorylation and activation of mTOR promotes cell growth, decreased apoptosis and increased angiogenesis. Because of PTEN's key role in mTOR activation, *PTEN* mutations have been exploited with use of mTOR inhibitors or PI3K inhibitors. Phase II trials using three mTOR inhibitors (temsirolimus, ridaforolimus, everolimus) have shown modest effects [76–78]. A phase I study demonstrated good tolerability when temsirolimus was combined with paclitaxel/carboplatin [79]. Currently, there are several trials assessing the combination of temisrolimus with chemotherapy and other agents including pegylated liposomal doxorubicin (PLD), bevacizumab, AMG386, and AZD2171, as well as an ongoing trial investigating the combination of ridaforolimus with carboplatin/paclitaxel. When everolimus combined with letrozole (aromatase inhibitor) (E/L) was evaluated in a phase II trial, a clinical benefit rate (CBR) of 40% was observed [77]. Data from an additional phase II study was recently presented at the 2018 SGO meeting comparing everolimus + letrazole to hormonal therapy, which showed that E/L is an active regimen in 24% of patients with recurrent endometrial cancer. PFS in the E/L arm was 6.4 months, while the PFS in the hormonal arm was 3.8 months. Response rate in the E/L arm in patients with no prior chemotherapy was 53% [80]. Given the complexity of the PI3K pathway, it is likely that agents that target only a single pathway node (such as mTORC1, AKT, PI3K) will not be effective due to crosstalk and feedback loops. It is important to note that to date, there has been minimal correlation seen between specific pathway mutations and response to this class of targeted therapies. Furthermore, combinations of mutations in other pathways may limit the effectiveness of targeting the mTOR pathway. As an example, one study suggested that KRAS mutations are associated with resistance to the mTOR inhibitor everolimus [81]. It is widely accepted that inhibition of multiple pathways may be required to achieve desired clinical responses. A study by Philip et al. suggested that inhibiting the PI3K-Akt-mTOR pathway sensitizes endometrial cancer cell lines to PARP inhibitors in patients with PTEN mutations [75]. *TSC2* mutations also affect the PI3K-Akt-mTOR pathway by activated mTORC1 signaling. In a recent study, *TSC2* mutations were found in 5.8% of patients with naïve advanced stage or recurrent endometrial cancer. Among those treated with temsirolimus (mTOR inhibitor), *TSC2* mutations were restricted to those with endometrioid histology and associated with an improved PFS [82].

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4.2. KRAS, BRAF, NRAS (Ras/Raf pathway)

Upstream activation of receptor tyrosine kinases stimulates the Ras/Raf pathway, and tumor dependency on activation of the pathway could lead to therapeutic vulnerabilities. Mutations in RAS, RAF, or MEK family members can activate the pathway, and MEK inhibitors have been explored in patients with activating mutations. A recent GOG phase II trial was undertaken to explore the MEK inhibitor, selumetinib, in recurrent endometrial cancer. Clinical responses were modest, with an objective response rate of 6% and 26% with stable disease [49]. Given the limited results with the single agent, additional studies are being done looking at MEKi in combination with other agents.

4.3. HRD pathway

Among gynecologic cancers, papillary serous ovarian cancer is the tumor type that is frequently characterized by homologous recombination deficiency (HRD). There is a body evidence that HRD defects may prove clinically relevant in endometrial cancers, specifically in the context of PTEN abnormalities, one of the most frequently observed molecular abnormalities in endometrial cancer. An association between PTEN deficiency and genomic instability was initially reported more than a decade ago [74]. Shen and colleagues demonstrated extensive genomic instability in PTEN mutant mouse cells associated with aberrant RAD51-mediated DNA double stranded break repair (DSBR) [83]. Abnormalities in cell cycle control in PTEN null cells also contribute to genomic instability independent of RAD51 [83]. PTEN deficiency in human tumor cells was shown both in vitro and in vivo to cause a homologous recombination (HR) defect. Mendes-Perieria and colleagues showed that *PTEN* mutant human cells, like mouse cells, had lower levels of RAD51 and that the PTEN deficient cells tumor were 20-fold more sensitive to PARP inhibitor exposure (olaparib) than the WT cells [84]. Similarly, PTEN mutant endometrial cancer cell lines have been reported to have increased sensitivity to PARP inhibitors. There is a report of a patient with recurrent metastatic endometrial endometrioid cancer that had a loss of PTEN but was BRCA1/2 wild-type who responded to olaparib for 8 months without progression of disease [85]. Ongoing studies evaluating the use of PARP inhibition in endometrial cancer are investigating biomarker response and resistance (NCT02208375; NCT02127151).

4.4. Implications for defects in two discrete DNA repair pathways

There is clear evidence that defects in the HRD pathway can help predict response to PARP inhibitors and other inhibitors that target cells with defects in the HRD pathway (i.e. ATR and ATM inhibitors). There have been conflicting studies regarding the use of microsatellite instability (MSI) and/or high mutational load (HML) as a predictor for response to HRD pathway inhibitors. One study investigated the role of MMR in ATR inhibition in HEC59 endometrial cancer cells deficient in MSH2 and showed that mismatch repair was not a useful indicator of synthetic lethality with ATRi or ATRi/cisplatin combination treatment [86]. As discussed previously, secondary mutations from mismatch repair deficiency can include defects in the double strand break repair gene *MRE11,* which is part of the MRN complex (MRE11/RAD50/NBS1). Another study looking at MRN complex loss via protein expression in endometrial cancer found that loss of MRE11 protein was found in 30.7% of endometrial cancers tested and showed that MRE11 depletion sensitized cell lines to treatment with a PARP inhibitor [87].

4.5. Other molecular aberrations of potential therapeutic significance

4.5.1. ARID1A

ARID1A is a tumor suppressor that play a key role in chromatin remodeling. Loss of ARID1A expression is common in endometrioid endometrial cancer at about 40% [88]. Several mechanism-guided approaches to treatment have been described for patients with ARID1A mutations. Data suggest that tumors with an ARID1A mutation could be sensitive to an EZH2 inhibitor [89]. EZH2 is overexpressed in endometrial cancer, including high grade type-2 tumors and basal-like subgroup of type-1 endometrioid endometrial cancers [90,91]. Overexpression of EZH2 is significantly associated with high histologic grade, angiolymphatic invasion, lymph node metastasis, myometrial invasion and cervical involvement [90,92]. In addition, ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cancer cells to PARP inhibitors in pre-clinical models [93]. ARID1A is recruited by ATR, localizes to sites of double strand DNA breaks and is a component of homologous recombination DNA double strand break repair [94]. Both EZH2 inhibitors and PARP inhibitors provide *potential* therapeutic strategies for patients with ARID1A-mutant tumors.

4.5.2. CTNNB1

CTNNB1, which encodes β-catenin, is commonly mutated in patients with endometrial cancer. The prognostic significance of mutations in *CTNNB1* is not entirely understood; however, these mutations can lead to activation of VEGF, which can explain the improved response in patients treated with bevacizumab [82]. A recent study showed mutations in *CTNNB1* in 26% of chemotherapy naive advanced stage or recurrent endometrial cancer. Patients with *CTNNB1*-mutated tumors treated with bevacizumab plus paclitaxel and carboplatin had longer PFS compared to those without mutations [82]. While *CTNNB1* mutations seem to be found more commonly in low-grade and low-stage endometrioid endometrial cancer patients who typically have good clinical outcomes, targeting the Wnt pathway could be beneficial in patients with recurrent or advanced cancers with *CTNNB1* mutations.

4.5.3. FGFR2

Fibroblast growth factor receptor 2 (FGFR2) has been shown to be activated in a number of cancers through a variety of mechanisms including gene amplification, translocations, and point mutations [95]. Predominantly in the endometrioid histological subtype, FGFR2 mutations have been shown to be associated with reduced disease free survival (DFS; hazard ratio [HR] = 3.24; 95% confidence interval, [CI] 1.35–7.77; $p = 0.008$) and overall survival (OS; HR = 2.00; 95% CI 1.09–3.65; $p = 0.025$) in early stage endometrioid EC (386 stage I and II cases) [96]. The prognostic importance of FGFR2 mutation was validated in a large, multi-institutional cohort from the GOG 210 clinical trial "*Molecular Staging of Endometrial Cancer*." [97] In a phase II study, single-agent FGFR2 inhibitor therapy showed limited activity and clinical response was not associated with FGFR2 mutation status [98]. There are on-going phase I trials looking at the use of FGFR inhibitors in all solid tumors. A recent review discusses the potential benefits and FGFR therapies [99].

4.5.4. HER2/neu

HER2/neu is a overexpressed in about 30% of uterine serous carcinoma, a rare, agressive variant of endometrial cancer. Trastuzumab is a humanized monoclonal antibody that targets HER2/neu. A phase II trial compared carboplatin/paclitaxel with and without trastuzumab in patients with advanced or recurrent uterine serous carcinoma who overexpress HER2/neu. The results of the study showed that the addition of trastuzumab to carboplatin-paclitaxel (experimental arm) was well-tolerated and resulted in increased PFS. The addition of trastuzumab to carboplatin-paclitaxel in HER2/neu-positive USC lead to a 56% decrease in risk of progression compared to carboplatin-paclitaxel alone. Furthermore, there was an increase in PFS with a median PFS of 8 months in the control group compared to 12.6 months in the experimental group. The greatest clinical benefit was seen in the upfront treatment setting in patients with stage III or IV disease. PFS was 9.3 months in the control arm versus 17.9 months in the experimental arm in these patients. Toxicity was no different between the control and experimental arms [100]. This study shows that targeting HER2/

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neu in a certain subset of patients may improve survival without increasing their risk for toxic side effects to treatment.

4.5.5. p53

As previously stated, *p53* mutations occur in 90% of endometriod endometrial carcinoma and 10–20% non-endometrioid endometrial carcinoma. Overexpression of *p53* is associated with high histological grade and advanced stage with an overall unfavorable prognosis. [59] A recent study attempted to combine molecular inhibitors such as bevacizumab (VEGF inhibitor) or temsirolimus (mTOR inhibitor) with chemotherapy in pateitns with stage III, Stage IVA, Stage IVB or recurrent endometrial cancer. They demonstrated a PFS of 19.6 months in patients with *p53* loss of function or null mutations treated with bevacizumab plus paclitaxel and carboplatin (Bev + PC) compared to 12.2 months PFS in the *p53* wild-type group treated with Bev + PC. The group treated with temsirolimus did not show increased PFS in patients with loss of function or gain of function mutations compared to wild-type [101].

5. Molecular markers that can guide treatment decisions

The previous sections provided a review of some of the specific mutations and genomic features characteristic of endometrial cancers that are relevant to planning use of adjuvant therapies for women with advanced disease. At present, molecularly guided management of endometrial cancers lags behind most other common cancers. In breast cancer, prognostic markers (primarily RNA profiling approaches) are in widespread use for deciding which women with early stage disease would benefit most from adjuvant therapies, or conversely be spared the adverse effects of adjuvant therapy given their low likelihood of recurrence. For advanced breast cancer, there are a variety of molecular marker guided treatment options approved for use in the US, many of which include combinations of targeted therapies. For lung cancer and many hematologic malignancies, biomarker-guided therapies are routine for patients with advanced and/or recurrent disease.

In endometrial cancer, the ***single*** approved marker-driven treatment option is pembrolizumab (immune checkpoint inhibitor) for tumors with defective MMR (tumor MSI or abnormal IHC findings). As noted, there is ***promise*** that agents that target specific mutations or pathway defects may prove valuable in the management of advanced stage endometrial cancers. These include but are not limited to PIK3CA pathway mutations (PIK3CA or mTOR inhibitors), ER/PR (hormonal therapy), PTEN mutations (mTOR inhibitors or PARP inhibitors), HRD (PARP inhibitors), ARIDIA mutations (EZH2 inhibitors, or PARP inhibitors) and FGFR2 mutations (FGFR inhibitors). The role of the VEGF inhibitor, bevacizumab, cannot be ignored in the discussion of treatment options for recurrent endometrial cancer. While no studies to date have been able to identify which patients' best respond to bevacizumab, there have been numerous trials that have included this agent in recurrent endometrial cancer and a number of on-going trials that are utilizing this targeted therapy. Single agent activity in endometrial cancer was demonstrated, and phase II studies have shown added activity with chemotherapy (GOG-86P and MITO END-2 trials) [50]. It seems likely that in the not too distant future, we will be able to better triage patients to specific therapies based on molecular signatures. Additional research, both retrospective and as part of prospective trials, will be critical in the development and implementation of precision/personalized medicine for women with endometrial cancers.

6. Germline and somatic tumor testing

We are in an era of genetic testing for inherited mutations applied both to germline and tumor DNA, and genomic profiling of tumors. Tumor IHC marker analysis is expanding, one example being use of p53 staining. The reduced cost of next generation sequencing (NGS) and improved informatics for mutation detections and other tumor features has resulted in more and more tumor analyses. The availability of NGS has allowed for clinicians to have access to genomic and molecular alterations in endometrial cancer that can identify women who are candidates for individualized targeted therapy. A study by Harada et al. showed the importance of the utilization of Molecular Tumor Board (MTB) in patient selection and assessment of treatment options for delivering precision medicine to cancer patients. They had 132 cases approved for testing with 34.8% of them having driver mutations that are associated with an active targeted therapeutic agent [102]. The uptake of testing is outpacing our ability to integrate data on treatment responses and molecular profiles within single institutions and across institutions. Patients are rapidly gaining knowledge about NGS and access to results and are demanding molecular testing from their physicians. Access to and the type of tumor typing performed is highly variable, but the use of NGS methods is near routine. NGS testing is likely to complement or replace currently used approaches to determining MMR status. It has been suggested that for colorectal cancers, total mutation load may be a clinically valuable surrogate for MSI or IHC testing in colorectal cancers [103]. What NGS testing and what read-out is most reliable for determining MMR status is yet to be established. At present, the FDA approval of pembrolizumab for all solid tumors that have MMR deficiency is based on MSI or IHC analysis performed in CLIA-certified laboratories. It is imperative that the correct (approved) tumor testing be performed as we move ahead with immune checkpoint treatments for advanced endometrial cancers. The "mutational load" surrogate was described by Stadler and colleagues for colorectal cancers [103]. Given the prevalence of MMR defects in endometrial cancer and differences in causes of MMR defects as well as differences is total mutation load, determining what the best methods are for analysis of endometrial cancers is critical to moving forward with NGS profiling. Gene panel tests for endometrial cancers may prove to be different than those most suited to other cancer types.

7. On-going and future trials

The number of gynecological cancer patients enrolling in clinical trials has significantly declined in the last 5–10 years, which has led to what The Society of Gynecologic Oncology (SGO) has named the "Clinical Trials Crisis." Since 2010, there has been a 90% reduction in women enrolled in NCI CTEP Gynecologic Cancer Phase III trials and the number of NCI CTEP-sponsored Gynecologic Oncology Available Clinical trials has decreased from 56 in 2012 to 18 in 2016 (www.gog.org). One of the factors that has contributed to this decline is the fact that there is currently a shifting emphasis to smaller biomarker-driven studies, with concomitant reduction of clinical trials. While the emphasis on biomarkers might have contributed to a reduction in the number of clinical trials, on a more positive note, it has allowed us to have more information about molecular signatures and genetic determinants leading to the development and spread of endometrial cancer. Additional biomarker driven clinical trials are needed in orderto identify more actionable mutations and targeted therapy to improve outcomes and survival of patients with endometrial cancer. Table 5 outlines the on-going current trials that are registered on clinicaltrials.gov in patients with advanced or recurrent endometrial cancer. While this does not include all the phase 1 and 2 trials that include endometrial cancer patients as part of larger trials, such as the NCI MATCH trial or the ASCO TAPUR trial, it does highlight some of the current novel therapies that are being tested in endometrial cancer and the combinations of agents that are being tried together. Cross-pathway combinations that are being explored in endometrial cancer include: PI3K/MEK, PARP/anti-angiogenic, PARP/PI3K, PARP or MEK or PI3K or anti-angiogenetic/immunotherapy, PI3K/hormonal. The challenge with many of these studies has been and will continue to be excessive toxicity; therefore, further pre-clinical and clinical research needs to be done to optimize the most effective combinations and to find predictive biomarkers for patients.

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Table 5
On-going clinical trials in advanced and/or recurrent endometrial cancer.

Drug(s)	Phase	Patient eligibility	Trial number
C + T ± Metformin	II, III	Stage III, IVA, IVB or recurrent EMCA	NCT02065687
Bev + C + T vs. C + Bev + Ixabepilone vs. T + C + Temsirolimus	II	Stage III, IVA, IVB or recurrent EMCA	NCT00977574
A + P + T vs. C + T	III	Stage III, stage IV or recurrent EMCA; estrogen receptor (ER)/progesterone receptor (PR) status	NCT00063999
Fulvestrant	II	Recurrent, persistent, or metastatic endometrial cancer that is not curable with surgery or radiotherapy	NCT00006903
C + T + Dasatinib	I	Stage III, stage IV, or recurrent EMCA	NCT01440998
P + T + C + RT	III	Stage III or IVA, stage I or II clear cell or serous carcinoma with positive peritoneal cytology	NCT00942357
Nivolumab ± Cabozantinib	II	Advanced, recurrent or metastatic EMCA	NCT03367741
P + RT + AZD1775	I	Stage I-III vaginal cancer, stage I-IIIB cervical cancer, stage I-IIIC uterine cancer	NCT03345784
Eribulin msylate + G	I	Recurrent or Stage III-IV endometrial or ovarian cancer	NCT00410553
Docetaxel + P	II	Stage IVb or recurrent EMCA	NCT01461759
Everolimus + Letrozole vs. Tamoxifen + Medroxyprogesterone	II	Stage III or IV or recurrent EMCA	NCT02228681
Letrozole + RAD001 (Everolimus)	II	Advanced or recurrent EMCA	NCT01068249
Metformin + Letrozole + Everolimus	II	Advanced or recurrent EMCA	NCT01797523
T + C + Selinexor 4 arms of 4 regimens using all 3 agents	I	Ovarian, fallopian tube or primary peritoneal cancer, endometrial cancer. EMCA must be stage IVB or recurrent disease	NCT02269293
Ribociclib + Everolimus + Letrozole	II	Advanced or recurrent endometrial carcinoma that is refractory to curative treatment	NCT03008408
Pembrolizumab + A	II	Advanced EMCA, prior platinum-based chemotherapy for first-line treatment has failed	NCT03276013
Enzalutamide + C + T	II	Stage III or IV or reccurent endometrioid EMCA	NCT02684227
Olaparib + metformin + cyclophosphamide	I, II	Recurrent EMCA after platinum-based therapy	NCT02755844
Nintedanib + C + T	II	Stage IIIC2, IVA, IVB and recurrent EMCA	NCT02730416
Letrozole ± Palbociclib	II	Advanced or recurrent EMCA	NCT02730429
Pembolizumab + T + C	II	Stage III or IV or recurrent EMCA	NCT02549209
ABTL0812 + T + C	I,II	Advanced, metastatic or recurrent EMCA and SCLC	NCT03366480
IMGN853 + Bev vs. IMGN853 + C vs. IMGN853 + PLD vs. IMGN853 + Pembrolizumab	I	Advanced ovarian cancer, primary peritoneal cancer, fallopian tube cancer, or EMCA	NCT02606305
T ± MLN0128, MLN0128 ± MLN1117	II	Advanced, recurrent, or persistent EMCA that has relapsed or is refractory	NCT02725268
C + cyclophosphamide + atezolizumab	I	Advanced breast or advanced gynecologic cancer	NCT02914470
Temsirolimus + Cediranib	I	Advanced gynecologic malignancies	NCT01065662
Vigil + Durvalumab	II	Locally advanced or metastatic women's cancer	NCT02725489
COTI2	I	Advanced or recurrent gynecologic malignancies	NCT02433626
Temsirolimus + nivolumab vs. Irinotecan + nivolumab vs. Irinotecan + capecitabine + nivolumab	I,II	Metastatic tumors (including EMCA)	NCT02423954
Pembrolizumab	II	Persistent or recurrent EMCA	NCT02899793
Niraparib	II	Recurrent EMCA	NCT03016338
LY3023414	II	Persistent or recurrent EMCA	NCT02549989
Brachytherapy + RT ± P	II	Recurrent EMCA	NCT00492778
Durvalumab ± tremelimumab	II	Recurrent or persistent EMCA	NCT03015129
Lenvatinib + T	I	Recurrent EMCA and ovarian cancer	NCT02788708
Tazemetostat	II	Recurrent ovarian, primary peritoneal and EMCA	NCT03348631
Trametinib ± GSK2141795	I	Recurrent or persistent EMCA	NCT01935973
Sunitinib malate	II	Recurrent or metastatic EMCA	NCT00478426
Durvalumab + RT ± tremelimumab	I	Metastatic or unresectable gynecologic cancers	NCT03277482
Letrozole + ribociclib	II	Recurrent ovarian, fallopian tube, primary peritoneal or EMCA	NCT02657928
G + mirvetuximab (IMGN853)	I	FRa-positive recurrent ovarian, primary peritoneal, fallopian tube, endometrial, triple negative breast cancer	NCT02996825
Surgery + HIPEC P → C or T or PLD or G (IP or IV at the discretion of the oncologist)	–	Stage III/IV primary or recurrent ovarian, fallopian tube, peritoneal carcinoma or EMCA	NCT01970722
Dasatinib	II	Recurrent or persistent ovarian, fallopian tube, endometrial or peritoneal cancer	NCT02059265
Sodium cridanimod	II	Recurrent or perisistent EMCA	NCT02064725
Epacadostat + pembrolizumab	II	Recurrent/metastatic EMCA	NCT03310567
Avelumab	II	MSS, MSI-H and POLE-mutate recurrent or persistent EMCA	NCT02912572
ONC201	II	Metastatic or recurrent EMCA	NCT03099499
Olaparib + AZD2014 (2 dosing regimens) vs. Olaparib + AZD5363	I,II	Recurrent endometrial, triple negarive breast and ovarian, primary peritoneal or fallopian tube cancer	NCT02208375
AL3818	I,II	Recurrent or metastatic endometrial, ovarian or cervical cancer	NCT02558348
Pembrolizumab + T + C	II	Stage III or IV or recurrent	NCT02549209
C + T vs. trastuzumab	II	Advanced/recurrent uterine serous papillary carcinoma	NCT01367002
AL3818 + C + T	I,II	Recurrent, persistent or metastatic endometrial, ovarian, fallopian, primary peritoneal or cervical carcinoma	NCT02584478

C = carboplatin, T = paclitaxel, A = Adriamycin/doxorubicin, Bev = bevacizumab, P = cisplatin RT = radiation therapy, PLD = pegylated liposomal doxorubicin hydrochloride, HIPEC = hyperthermic intraperitoneal chemotherapy, G = gemcitabine.

8. Conclusion

There has been an explosion of enthusiasm for understanding both the germline and tumor mutation status of endometrial cancer patients along with its potential clinical application. Molecular testing methods are evolving rapidly and genomic science is moving faster than clinicians are able to keep up with. There is real promise that targeted therapy will improve outcomes for women with endometrial cancer. It is, however, of paramount importance that clinicians understand the significance and limitations of knowledge that is being disseminated to researchers, care providers and directly to patients. It will be critical for gynecologic oncologists to work with basic and translational

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researchers to better understand what molecular alterations are driving the progression of endometrial cancer and how they contribute to biologic aggressiveness and response to treatments. Without multidisciplinary and multi-institutional collaboration, progress and success with development of rationale biomarker-driven therapeutic combinations will be limited. Given that the precision medicine field is rapidly moving forward and the amount of genomic information and access to molecular data is beyond what it has ever been before, it is imperative that we continue to develop our skills and our ability to interpret the vast amounts of data. The importance of having clinicians, basic scientists, clinician-scientists, advanced practitioners, clinical trial researchers, molecular pathologists, academicians, industry, and genetics counselors who work to educate each other and the patients has never been greater. It is imperative that we as physicians, and in particular specialists in gynecologic oncology and allied disciplines, maximize how our collective knowledge can be used to improve outcomes of our patients with endometrial cancer.

Conflicts of interest

The authors declare no potential conflicts of interest.

Author contribution

All authors contributed to data collection, manuscript drafting and revising and manuscript editing.

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