Gynecologic Oncology 153 (2019) 175–183

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Endocrine therapy in endometrial cancer: An old dog with new tricks

Katarzyna J. Jerzak [a], Linda Duska [b], Helen J. MacKay [a,*]

[a] Division of Medical Oncology and Hematology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[b] Division of Gynecologic Oncology, University of Virginia, Charlottesville, VA, United States of America

HIGHLIGHTS

- A high proportion of endometrioid endometrial cancers are estrogen receptor (ER) and/or progesterone receptor (PR) positive.
- Responses of endometrial cancers to single-agent progestins, selective ER modulators and aromatase inhibitors are low.
- Understanding mechanisms of resistance to endocrine therapy has generated opportunities to enhance responses to treatment.
- Clinical trials evaluating novel combination therapies are highly desirable to optimize ER/PR targeted treatment approaches.

ARTICLE INFO

Article history:
Received 13 November 2018
Received in revised form 15 December 2018
Accepted 17 December 2018
Available online 5 January 2019

Keywords:
Endocrine therapy
Endometrial cancer
Resistance mechanisms

ABSTRACT

One of the most prevalent potential therapeutic targets for women with endometrioid endometrial cancer (EC) is the estrogen receptor (ER)/progesterone receptor (PR) pathway. Despite a high proportion of endometrioid ECs being ER and/or PR positive, endocrine therapy is only effective in a minority of women with EC and ultimately patients progress with resistance developing to treatment. A variety of treatment approaches with progestins, selective ER modulators (SERMs) and aromatase inhibitors (AIs) are available. Exploration of these agents is desirable given their favorable toxicity profile. Greater understanding of ER and PR biology may help identify patient populations who will derive benefit and strategies for new therapeutic options. Here we review the clinical efficacy of endocrine therapy in EC, discuss the role of ER and/or PR as prognostic biomarkers, describe disease-specific mechanisms of resistance to endocrine therapy and explore potential strategies to enhance response for the "next generation" of endocrine therapy clinical trials. We also describe the use of endocrine therapy in younger women seeking to pursue fertility sparing options for management of EC.

Contents

1. Introduction . . . 176
   1.1. Efficacy of endocrine therapy in EC . . . 176
      1.1.1. Progestins. . . . 176
      1.1.2. Selective estrogen receptor modulators . . . 177
      1.1.3. Selective estrogen receptor degrader (SERD) . . . 177
      1.1.4. Aromatase inhibitors . . . 177
      1.1.5. Others . . . 177
   1.2. Endocrine therapy as treatment in fertility preservation . . . 177
2. Biomarkers for endocrine therapy in EC . . . 177
3. Potential therapeutic targets to optimize endocrine therapy in endometrial cancer . . . 179
   3.1. Epigenetic modulation . . . 180
      3.1.1. Histone deacetylating inhibitors (HDACs) . . . 180
      3.1.2. Demethylation . . . 180
      3.1.3. Histone methylation inhibitors . . . 180
   3.2. Phosphoinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) . . . 180

* Corresponding author.
E-mail address: helen.mackay@sunnybrook.ca (H.J. MacKay).

https://doi.org/10.1016/j.ygyno.2018.12.018
0090-8258/

3.3. Cell cycle pathways . . . 180
3.4. Androgens . . . 181
3.5. Insulin/metabolic factors . . . 181
3.6. The immune microenvironment . . . 182
4. Future directions . . . 182
Conflict of interest statement . . . 182
Author contributions . . . 182
Acknowledgements . . . 182
References . . . 182

1. Introduction

The incidence of endometrial cancer (EC) is increasing worldwide. In the United States, the estimated annual incidence of EC in 2013 was 49,560 rising to 63,230 cases in 2018 [1]. If current trends continue, there may be as many as 130,000 new cases of EC per year by 2030 [2]. These statistics reflect an aging population (median age at diagnosis of EC is 63), a rise in the incidence of obesity and type II diabetes, delays in the age of child-bearing and a decrease in the rate of hysterectomy for benign disease [3]. Approximately 14% of EC cases will be diagnosed in pre-menopausal women and this number is increasing [4]. For younger women, fertility sparing treatment options are important and considered for low grade tumors without myometrial invasion.

The majority of women, irrespective of age, are diagnosed with early stage EC and surgery is the mainstay of treatment. Although the prognosis for most women is good, treatment options for those diagnosed with advanced, recurrent or metastatic disease are limited and survival has remained unchanged over the last few decades [1]. Much excitement has been generated in the last few years by advances in our molecular understanding of EC and its potential to lead to better treatment options for patients. In 2013, The Cancer Genome Atlas (TCGA) project identified four molecular subtypes of EC based on common genomic features: (i) ultramutated polymerase epsilon (POLE), (ii) hypermutated microsatellite instability (MSI), (iii) copy number abnormalities-low, and (iv) copy number abnormalities high groups [5]. This provided an impetus for further research and for development of new therapeutic directions [6]. Expansion in our knowledge regarding MSI high tumors ultimately established immunotherapy as a new standard of care for the second line treatment of patients with MSI high EC [7]. Exploration of immunotherapy combinations and drugs targeting DNA repair and other molecular features of EC are active areas of research.

However, in all of the excitement generated by these emerging data, there has been a tendency to overlook the potential of the original "targeted therapy" in EC, endocrine therapy. Active recruiting trials listed on Clinicaltrials.gov (October 2018) include 107 studies open for EC patients investigating targeted, immune or chemotherapy combinations compared to just 12 with endocrine therapy (including fertility preservation studies). Optimizing and building on the role of endocrine therapy in EC is attractive for many reasons. Rising rates of obesity are associated with increases in low grade endocrine receptor positive cancers [8]. Endocrine therapy is well tolerated with a known toxicity profile, which is important given that EC patients are often older with multiple co-morbidities. Indeed, identifying well tolerated therapeutic combinations that can maintain quality of life may be relevant not only in the advanced setting but also for adjuvant treatment, an area under explored in EC [9]. In addition, because the risk-to-benefit ratio is acceptable prior to definitive surgery, endocrine therapy is suitable for exploration in Window of Opportunity style studies, which are designed to assess surrogate and pharmacodynamic end points. Finally, the use of endocrine therapy in younger women seeking to pursue fertility sparing options is a well-established and unique area of research in this disease.

Here we review the clinical efficacy of endocrine therapy in EC, explore potential strategies to enhance response and highlight potential for the "next generation" of endocrine therapy clinical trials.

1.1. Efficacy of endocrine therapy in EC

The first reports of benefit from endocrine therapy (medroxyprogesterone) in the treatment of advanced EC appeared in the 1960s [10]. However, despite nearly 6 decades of studies in EC many fundamental questions remain unanswered. Unlike breast cancer, the clinical benefit for endocrine therapy in EC has not been fully defined. The lack of randomized trial data prompted the authors of the 2010 Cochrane review to conclude there was no evidence that endocrine therapy improved survival in EC [11]. Furthermore, the ability to demonstrate improvement in quality of life and symptom control was insufficiently evaluated to draw any conclusions.

Despite this, endocrine therapy is a part of routine clinical care particularly for patients with low grade EC [12]. In a recent systemic review and meta-analysis that included 9 trials and 1837 patients, the authors conclude that there is a modest benefit for endocrine therapy with a response rate of 21.6% in the frontline setting, median Progression Free Survival (PFS) of 2.8 months and a median Overall Survival (OS) of 10.2 months [13]. Interpretation of this data remains challenging, however, due to inclusion of small, mixed EC population trials with differing response criteria and variable durations of follow-up. Furthermore, although estrogen (ER) and progesterone (PR) receptors have demonstrated some utility as predictive biomarkers, they have not been routinely incorporated into clinical trials. Studies either did not provide subgroup data according to ER and/or PR status or, where this was available, there was no standardized methodology or cut offs defined. While in more recent trials there have been improvements, future trials need to specify methodology and pre-analytics, define cut offs and report subgroup analyses based on the expression of ER and PR. Given the relative lack of efficacy compared to breast cancer, exploration beyond ER and PR status is warranted to better understand activity of endocrine therapy in the context of ER and PR related pathways in EC.

It is unclear whether patients with EC should be re-treated with endocrine therapy post progression on an endocrine agent and what benefit (if any) would be expected [14]. The value of sequencing different classes of endocrine therapy is also of practical interest but data are lacking. One study examined alternating megestrol acetate with tamoxifen as a means of increasing PR expression [14]. This GOG trial reported a response rate of 27% with an OS of 14.7 months, suggesting that timing and sequencing of endocrine therapies may be of interest [14]. Further work, including sequential examination of tumor tissue is necessary to better understand EC biology. Window of Opportunity studies may provide information relevant to future therapeutic trial design and could potentially act as a "screen" to identify pharmacodynamically active combinations. Sequential biopsies within therapeutic trials to understand the impact of chronological heterogeneity on response would also be of interest.

Specific classes of endocrine agents used to treat, predominantly, low grade EC include: progestins, selective ER modulators (SERMs), selective ER degraders (SERDs) and aromatase inhibitors (AIs).

1.1.1. Progestins

Multiple small studies demonstrated clinical benefit of progestins but variable response rates have been documented depending on the

route of administration (IM versus oral), tumor grade, histology, PR expression status and the line of therapy (i.e. first or subsequent exposure to endocrine therapy). Among 13 studies evaluating the efficacy of progestational agents in the first line setting the response rate was 23.3%, with 12.0% achieving a CR and 45.8% experiencing a clinical benefit from therapy [13]. Median PFS was 2.9 months and the OS was 9.2 months [13]. When taken in the context of the 6 studies that reported response based on PR status, the response rate was 35.5% in PR positive tumors compared to 12.1% with PR negative tumors [13]. Dose did not appear to impact response to medroxyprogesterone acetate when evaluated in a study including 299 women randomized to receive either 200 mg/day or 1000 mg/day [15]. In this trial, higher levels of PR expression (>50 fmol/mg cytosol protein) were associated with a greater chance of response [15].

In a window-of-opportunity study conducted by the GOG, down regulation of ER and PR receptors was observed following 21–24 days of medroxyprogesterone prior to definitive surgery [16]. In this study involving 59 women, one complete histologic response was observed and 37 patients (63%) had a partial response [16]. In addition, intrauterine levonorgestrel demonstrated efficacy among post-menopausal women with atypical hyperplasia/endometrial intraepithelial neoplasia (AH) or grade 1 endometrioid EC, with a high rate of CR (50%) and a PR rate of 8%; among those women who achieved a CR, 22% ($n = 4/18$) experienced recurrence of hyperplasia or cancer during a median follow-up of 42 months (range 3–118 months) [17]. Hence, the authors conclude that this strategy of intrauterine levonorgestrel may be considered among post-menopausal women with AH or grade 1 endometrioid EC who are poor candidates for standard surgical management [17].

Unfortunately, progestins have proven disappointing when evaluated in unselected EC populations in the adjuvant setting with no clear benefit emerging for their use [9].

1.1.2. Selective estrogen receptor modulators

The SERM, tamoxifen, has been evaluated in the 2nd line metastatic EC setting with an ORR of 20.6%, 36.3% Clinical Benefit Rate (CBR) and a 6.3% rate of Complete Response (CR) [13]. It is notable, however, that SERMS serve as agonists in endometrial tissue and that they have a well-established risk of venous thromboembolism.

1.1.3. Selective estrogen receptor degrader (SERD)

Fulvestrant is an example of a pure estrogen antagonist with a high affinity for ER. This drug has been studied in two EC trials with response rates of 11% to 16% [13], but lack of trials using an optimized dose of 500 mg preclude definite conclusions regarding benefit in EC.

1.1.4. Aromatase inhibitors

Aromatase inhibitors (AIs) inhibit the aromatase enzyme and reduce the peripheral conversion of androgens to estrogen in post-menopausal women. Two window of opportunity studies have demonstrated that AIs (letrozole and anastrozole) have a biological effect on EC tissue, reducing the expression of ERα, PR and the androgen receptor (AR) [18,19].

Clinical benefit of AIs has been demonstrated in EC. In the EC arm of the PARAGON trial for ER/PR positive gynecologic cancers demonstrated a CBR of 44% and median PFS of 3.2 months [20]. Further, responders had significant improvements in quality of life, including domains of emotional and cognitive functioning [21]. However, contrary to observations in ER+ breast cancer, response rates in all-comers using letrozole, exemestane and anastrozole were low [13] and support the theory that there may be differences in the aromatase enzyme in EC [22].

1.1.5. Others

Gonadotrophin releasing hormone (GnRH) analogues have been studied in both first- and second-line treatment of EC with similar responses to the other endocrine therapies [13]. Their subcutaneous or intramuscular delivery makes them more uncomfortable for patients in the short term, however compliance may be improved.

It is also noted that inhibition of the steroid sulphatase (STS) enzyme, which is involved in the formation of estradiol and androstenediol, has been investigated in EC. A phase II trial explored the anti-cancer activity of irosustat, an STS inhibitor, among 36 women with advanced or recurrent ER+ EC but failed to show sufficient activity to warrant further investigation [23].

1.2. Endocrine therapy as treatment in fertility preservation

Women with low grade EC wishing to preserve fertility can be managed with high dose oral progestins and/or levonorgestrel-release intrauterine devices (LNG-IUD). A systematic review and meta-analysis of 32 studies found a pooled regression rate of 76% and a recurrence rate of 41% [24]. A further systematic review of mostly observational studies reported a response rate of 48% with 25% of women having persistent disease [25]. In addition, a study using data collected from the SEER data base (1993–2012) demonstrated that at 15 years there was no difference in all-cause mortality among young women who were managed conservatively compared to those who underwent surgery for low grade EC [26]. Prospective studies evaluating the use of progesterone IUDs are currently ongoing (Table 1).

The impact of obesity and weight reduction on endometrial hyperplasia and early EC has been reported by several investigators. MacKintosh et al. reported on a series of 72 women (including older patients, age range 24–65) who underwent bariatric surgery for class III/IV obesity [27]. Baseline biopsies revealed EC in 4 women and atypical hyperplasia in 6; following bariatric surgery and weight loss, atypical hyperplasia had resolved in 5 out of 6 cases [44]. Global ER and PR levels of expression were lower in EC tissue following weight loss along with markers of proliferation, but there were no changes in serum estradiol or progesterone, suggesting that alternate mechanisms to reduced hormone production could be acting in these women [27]. Regardless, the potential to combine weight loss with endocrine therapy to optimize treatment and health related benefits among women with early, low grade EC is an attractive one. Several studies are exploring the combination of LNG IUD or progestin therapy in combination with weight loss and/or metformin in obese women [28]. A validated, TCGA-inspired Proactive Molecular risk classifier for Endometrial Carcinoma (ProMisE) may be of value when counselling women regarding the relative risks and benefits of pursuing such fertility-preserving treatment strategies; its independent prognostic association with OS and disease-specific survival among young women <50 years of age is particularly appealing in this setting [29,30].

Ongoing investigation of appropriate (non-teratogenic) combinations in fertility preservation clinical trials is important for the increasing number of young women diagnosed with EC and precursor lesions.

2. Biomarkers for endocrine therapy in EC

While ER and PR status have been evaluated in a limited manner with regard to *predicting* response to treatment, ER and PR status are known to be prognostic in EC. In a recent meta-analysis, higher levels of ER expression were associated with longer OS (HR 0.75, 95% CI 0.68–0.83), longer cancer-specific survival (HR 0.45, 95% CI 0.33–0.62) and PFS (HR 0.66, 95% CI 0.52–0.85) [31]. Higher levels of PR were also associated with longer OS (HR 0.63, 95% CI 0.56–0.71), cancer specific survival (HR 0.62, 95% CI 0.42–0.93) and PFS (HR 0.45, 95% CI 0.30–0.68) [30]. Similar results were seen in the large prospective Molecular Markers in Treatment of Endometrial Cancer (MoMaTEC) study [32]. In studies that are limited to ER and PR positive patient populations, the increased PFS and OS in these groups need to be accounted for in the statistical design; furthermore, there is a preference for randomized trials when endocrine therapy combinations are being

Table 1
Currently open clinical trials that are evaluating pharmacologic, endocrine targeted therapies in endometrial cancer and pre-malignant lesions.

Title (NCT number)	Conditions	Interventions
Megestrol acetate with or without pterostilbene in treating participants with endometrial cancer undergoing hysterectomy (NCT03671811)	• Endometrial carcinoma	Dietary supplement Drug: megestrol acetate
Evaluating cancer response to treatment with abemaciclib and Fulvestrant in women with recurrent endometrial cancer (NCT03643510)	• Endometrial adenocarcinoma	Drug: Fulvestrant Drug: abemaciclib
Fertility-sparing management using high-dose oral progestin in young women with endometrial cancer (NCT03567655)	• Endometrial cancer	Drug: Farlutal tab. 500 mg/Pfizer
Effect of fertility-sparing therapy of early endometrial cancer (NCT03538704)	• Endometrial cancer	Drug: metformin
Value of LNG-IUS as fertility-preserving treatment of EAH and EC (NCT03463252)	• Endometrial cancer • Atypical endometrial hyperplasia	Drug: progesterone Device: Mirena® Drug: GnRH agonist
Exemestane in treating patients with complex atypical hyperplasia of the endometrium/endometrial intraepithelial neoplasia or low grade endometrial cancer (NCT03300557)	• Atypical hyperplasia • Endometrial intraepithelial neoplasia • Grade 1 endometrial endometrioid adenocarcinoma • Grade 2 endometrial endometrioid adenocarcinoma	Drug: exemestane
Megestrol acetate plus LNG-IUS in young women with early endometrial cancer (NCT03241914)	• Endometrial neoplasm malignant stage I	Drug: megestrol acetate Device: levonorgestrel-releasing intrauterine system (LNG-IUS)
An endometrial cancer study for women with recurrent or persistent endometrial cancer (NCT03077698)	• Endometrial cancer	Drug: sodium cridanimod Drug: progestin therapy
Study of the CDK4/6 inhibitor palbociclib (PD-0332991) in combination with the PI3K/mTOR inhibitor gedatolisib (PF-05212384) for patients with advanced squamous cell lung, pancreatic, head & neck and other solid tumors (NCT03065062)	• Lung cancer squamous cell • Solid tumors • Head & neck cancer • Pancreatic cancer	Drug: palbociclib Drug: gedatolisib
Medroxyprogesterone acetate with or without entinostat before surgery in treating patients with endometrioid endometrial cancer (NCT03018249)	• Grade 1 endometrial endometrioid adenocarcinoma • Grade 2 endometrial endometrioid adenocarcinoma • Grade 3 endometrial endometrioid adenocarcinoma • Uterine corpus adenosarcoma	Drug: entinostat Procedure: hysterectomy Drug: medroxyprogesterone acetate
Study of ribociclib (LEE011), everolimus, and letrozole, in patients with advanced or recurrent endometrial carcinoma (NCT03008408)	• Malignant neoplasms of female genital organs • Endometrial carcinoma	Drug: ribociclib Drug: everolimus Drug: letrozole
Hormone receptor positive endometrial carcinoma treated by dual mTORC1/mTORC2 inhibitor and anastrozole (NCT02730923)	• Endometrial carcinoma • Metastatic carcinoma • Hormone receptor positive tumor	Drug: AZD2014 Drug: anastrozole
Trial of letrozole + palbociclib/placebo in metastatic endometrial cancer (NCT02730429)	• Endometrial cancer	Drug: palbociclib/placebo Drug: letrozole
Enzalutamide in combination with carboplatin and paclitaxel in endometrial cancer (NCT02684227)	• Endometrial cancer	Drug: enzalutamide Drug: carboplatin Drug: paclitaxel
Open-label phase 1b study of ARQ 092 in combination with anastrozole (NCT02476955)	• Solid tumors • Ovarian cancer • Endometrial cancer	Drug: ARQ 092 + carboplatin + paclitaxel (closed) Drug: ARQ 092 + paclitaxel (closed) Drug: ARQ 092 + anastrozole
Phase II study of intrauterine device (IUD) alone or in combination with everolimus in endometrial cancer (NCT02397083)	• Endometrial cancer	Device: levonorgestrel intrauterine device (LIUD) Drug: everolimus Behavioral: questionnaire
Metformin with the levonorgestrel-releasing intrauterine device for the treatment of complex atypical hyperplasia (CAH) and endometrial cancer (EC) in non-surgical patients (NCT02035787)	• Complex atypical hyperplasia • Endometrial cancer	Drug: metformin
Improving the treatment for women with early stage cancer of the uterus (NCT01686126)	• Complex endometrial hyperplasia with atypia • Grade 1 endometrial endometrioid adenocarcinoma	Drug: levonorgestrel Drug: metformin
High-dose megestrol in treating patients with metastatic breast cancer, endometrial cancer, or mesothelioma (NCT00002465)	• Breast cancer • Endometrial cancer • Malignant mesothelioma	Drug: megestrol acetate

evaluated to avoid overestimation of the therapeutic benefit over endocrine therapy alone.

Compared to breast cancer the response to endocrine therapy is lower than one would predict in hormone receptor positive EC. To better understand which patients with EC may benefit from endocrine therapy, investigators may need to go beyond simple receptor IHC status for ER and PR. For example, it has been proposed that specific isoforms of PR (PR-A and PR-B, both encoded on chromosome 11) may be relevant. Based on selective ablation studies in a mouse model, PR-B is felt to contribute to estrogen and progesterone-induced endometrial proliferation whereas PR-A inhibits it [33]. A third PR-C isoform lacks a ligand binding domain, and hence, may serve as a constitutive antagonist of progesterone-mediated endometrial proliferation [33]. Among the studies that measured levels of PR-A ($n = 5$) and PR-B ($n = 3$) isoforms, higher PR-A but not PR-B expression was prognostic for favorable PFS (HR 0.60; 95% CI 0.43–0.82, $p = 0.001$) with a trend for an OS benefit [HR 0.67, 95% CI 0.49–0.90, $p = 0.066$] [31]. Unfortunately, distinguishing PR isoforms via IHC is problematic because PR-B and PR-A are identical, apart from a unique sequence of amino acids that is present at the NH2-terminal domain of PR-B; while antibodies to detect the unique component of PR-B are available, quantifying PR-A specifically continues to pose a challenge [34]. Ultimately

evaluation of activated PR rather than total PR may yield interesting biomarkers or a biomarker signature, but a validated measure has yet to be developed. This requires evaluation of mRNA and proteins associated with PR activity.

Indeed, the biology of PR is complex; its diverse effects include down-regulation of ER, paracrine induction of 17-β HSD in endometrial cells by the stroma (ultimately converting 17-β estradiol to estrone), as well as the inhibition of estrogen-responsive gene expression [35]. Non-genomic effects of progesterone receptors have recently been reviewed by Garg et al. [36], involving alterations in cAMP levels, activation of the MAPK pathway, as well as stimulation of phospholipase C (PLC), protein kinase G (PKG) and protein kinase C (PKC) (Fig. 1). Hence, the relative "strength" of progesterone's biologic effects in any individual woman with EC is multi-factorial. The tumor microenvironment and cross talk with other hormonal pathways may also contribute to PR's biological actions and the net-effect of treatment with progestational agents.

Approximately 80% of EC express ERα [37], which is encoded by the estrogen receptor 1 (ESR1) gene [36]. ERα binding sites are highly conserved between tamoxifen associated EC and breast cancer but differ in non-tamoxifen induced EC [37]. Baxter et al. investigated phosphorylated ERα as a marker of transcriptional activation in TCGA data sets in EC and breast cancer [37]. Transcriptomic pathway analysis suggested that non-classical ERα-signalling may be more important in EC and that the estrogen associated transcriptome is tissue-specific. Hence, exploration of ERα accompanied by transcriptional signalling data may assist in the identification of a more appropriate biomarker signature in EC.

It is also notable that approximately 16% of EC in the TCGA dataset have an amplification encompassing or overlapping ESR1, which truncates the ligand binding domain in approximately 20% of cases [38]. Other alterations in ESR1 such as point mutations, and splice variants have also been described [39]. This is relevant because ECs that are unable to bind estradiol may display estrogen-independent growth patterns, making downstream elements of the ER pathway, alone or in combination with conventional endocrine therapy, a potentially attractive therapeutic strategy. Although these genomic changes in ESR1 have only been identified in 2.8% of primary EC [39], it is possible that this incidence is higher in the setting of recurrent EC and/or endocrine-resistant tumors due to disease evolution through selective treatment pressure. Thus, ESR1 status in EC may be of interest to study in the context of response to endocrine therapy. The fact that such mutations can be identified in circulating DNA opens the possibility of future blood-based predictive biomarkers in EC.

In the context of molecular subgroups of EC, initially identified by the TCGA and later by paired down classifiers developed by groups in Vancouver and Leiden, ER and PR expression (evaluated by immunohistochemistry with defined cut offs) is seen across all molecular phenotypes [8,40]. Karnezis et al. reported that ER expression was common across all subgroups - 73.9% mismatch repair deficient (MMR-D); 75.7% POLE; 67.4% P53 abnormal and 92% p 53 WT [8]. PR positivity was observed again across the subgroups but was more common in p53WT (60.9 MMR-D; 75% POLE; 83.9% P53WT and 44.7% P53 abnormal) [8]. Molecular analyses of early stage EC from the PORTEC cohorts suggested that hormone receptor negative tumors were more likely to occur in the P53 abnormal subgroup [40]. These data suggest that while ER/PR status may help to stratify risk within molecular subgroups, designing trials for endocrine therapy for specific molecular subtypes of EC is not likely to be a successful strategy, with the possible exception of excluding patients with p53 abnormal tumors if an enriched, mixed population of endocrine receptor positive patients is required.

3. Potential therapeutic targets to optimize endocrine therapy in endometrial cancer

Developing therapeutic strategies, based on EC biology, that increase responsiveness to endocrine therapy is an attractive proposition. There are several mechanisms that have the potential to increase efficacy.

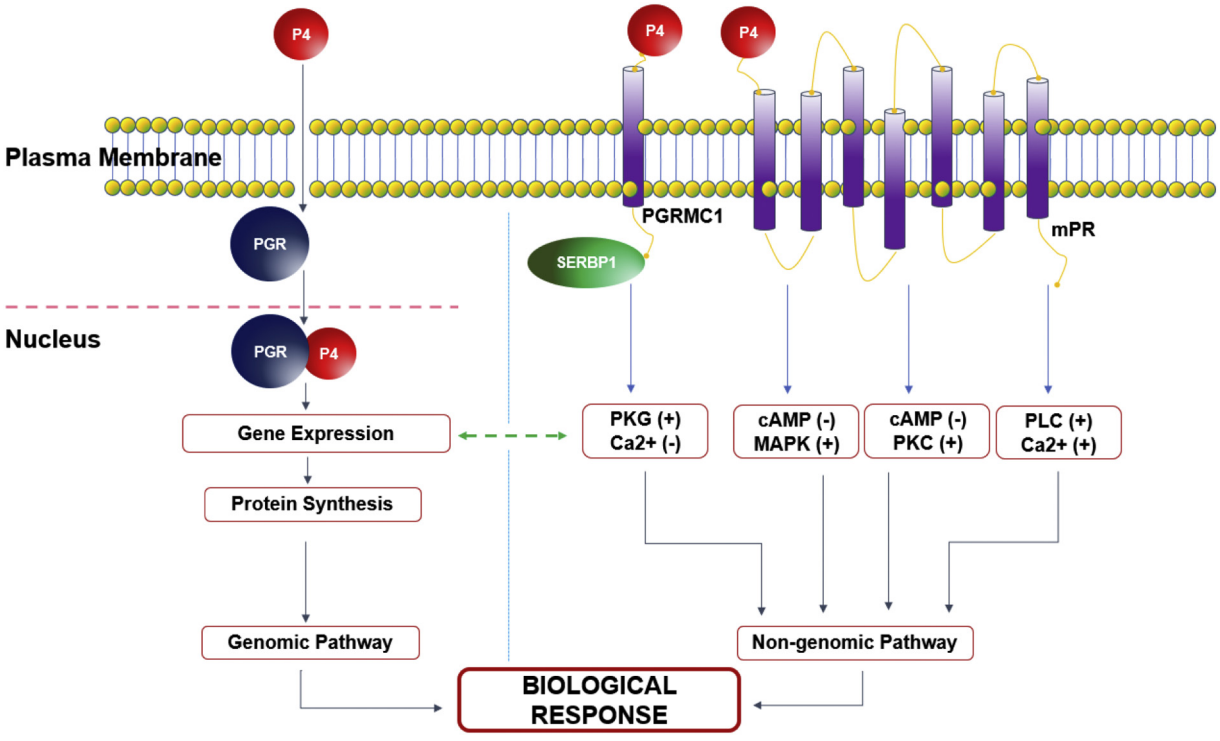

Fig. 1. Genomic and non-genomic effects of progesterone (P4) in the cell. In the genomic pathway, P4 binds to the nuclear progesterone receptor (PGR), which ultimately influences gene expression and protein synthesis. In the non-genomic pathway, P4 may bind to progesterone receptor membrane component 1 (PGRMC1) and complex with serpine mRNA binding protein 1 (SERBP1) to activate protein kinase G (PKG) and reduce the calcium level (Ca^{2+}) in the cell. P4 may also bind to membrane progesterone receptors (mPRs) to stimulate phospholipase C (PLC), protein kinase C (PKC) and the mitogen activated protein (MAP) kinase pathways.
(Adapted from Kowalik et al. [35]).

3.1. Epigenetic modulation

Silencing of ER and/or PR has been extensively reported in EC secondary to epigenetic modification.

3.1.1. Histone deacetylating inhibitors (HDACs)

HDACs increase acetylation of histones, thereby unwinding DNA and exposing promoter regions for transcription of genes such as the ER [41]. In addition, HDAC inhibitors such as entinostat are also proposed to have pleotropic effects, including an increase in DNA damage by reactive oxygen species (ROS), as well as effects on other targets such as p53, PARP, NFkB and HIF-1α [41].

Multiple pre-clinical studies have demonstrated anti-proliferative effects of HDAC inhibitors and their ability to restore functional PR expression has been confirmed in EC cell lines [42]. In vitro and in vivo EC models demonstrate that the addition of entinostat to progesterone induces PR dependent genes associated with endometrial differentiation while inhibiting genes associated with proliferation including ER-alpha (ESR1) and Myc [42]. Furthermore, there is the possibility that in tumors with low levels of PR, increasing PR expression may increase responsiveness. As proof of principle, the NRG window of opportunity study GY011 investigated the combination of entinostat and medroxyprogesterone in EC. The trial has completed accrual and tumor samples are undergoing analysis.

3.1.2. Demethylation

Several in-vitro studies have demonstrated that reversal of promoter methylation can increase the expression of ER using DNA methyltransferase (DNMT) inhibitors. For example, treatment with 5-AzaC reversed the methylation of ER and PR isoforms in EC cell lines, resulting in expression of both ER and PR [43].

3.1.3. Histone methylation inhibitors

Enhancer of zeste homolog 2 (EZH2), the catalytic subunit of polycomb repressive complex 2 (PRC2), trimethylates histone H3 on lysine 27 resulting in the suppression of PR gene expression, [44]. EZH2 overexpression in EC is associated with increased proliferation and invasion, high tumor stage and grade, and decreased survival [44]. Further, pre-clinical studies using EZH2-specific inhibitors showed decreased EC cell growth and invasion in vitro and decreased tumor growth in mouse model systems [44]. Together, these observations indicate that EZH2 may regulate EC through the downregulation of PR expression.

It is unclear whether targeting one (or potentially more) epigenetic modification mechanisms in combination with endocrine therapy will improve outcome for women with EC in the clinic. In pre-clinical models, Yang et al. found that HDAC inhibition (using LBH589) was more effective than DNMT inhibition (using 5-aza-deoxycytidine) in restoring PR expression in both Ishikawa and ECC1 cell lines [42]. While the combination of LBH589 and 5-aza-deoxycytidine restored PR expression slightly more than LBH589 alone in ECC1 cells, the expression of PR significantly *decreased* with combination therapy in Ishikawa cells [42]. These preclinical studies suggest studying epigenetic modulation in combination with endocrine therapy should occur sequentially and include high quality correlative studies to understand both tumor biology and the impact of changes in epigenetic regulation in relation to response.

3.2. Phosphoinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)

The ER isoforms have both transcriptional and non-genomic functions. In EC, estradiol signalling is mediated through ERα and is capable of activating the mitogen activated protein kinase (MAPK) signalling pathway, which further activates downstream molecules ERK and AKT (part of the PI3K/AKT MTOR pathway) [45]. PR signalling also partially acts through the MAPK and PI3K/AKT/mTOR pathways [46] suggesting that targeting these downstream elements in conjunction with endocrine therapy is of interest. The rapalog class of mTOR inhibitors have been evaluated in several single-arm EC trials, but given cross talk between the PI3K/AKT/mTOR and the ER pathways, investigation of the combination of an mTOR inhibitor (everolimus) and letrozole was undertaken in women with EC [47]. In a phase II single-arm study of everolimus and letrozole, 35 women with advanced EC who received up to two prior cytotoxic lines of therapy were evaluable for a response [47]. Although the median PFS was only 3.0 months (95% CI 1.9–-15.7 months), the clinical benefit rate (CBR) at 16 weeks was 40%, the RR was 32% and 9 patients (26%) had a CR [47]. Furthermore, the combination was well tolerated [47]. Of interest, 4 patients with endometrioid EC and a CTNNB1 mutation had either a CR ($n = 3/4$, 75%) or SD ($n = 1/4$, 25%), suggesting that degradation of its B-catenin protein product and resultant aberrations in the Wnt signalling pathway may render ECs susceptible to mTOR inhibition [47]. As in other single agent rapalog studies, PIK3CA does not appear to predict response to mTOR inhibition in EC [48].

A further study by Soliman et al. added metformin to letrozole and everolimus reporting a clinical benefit rate (PR + SD) of 60% and this combination was well tolerated [49]. Of note, however, a clinical trial combining an mTOR inhibitor with alternating megestrol acetate and tamoxifen did not have incremental activity and was associated with a high rate of thromboembolism [50]. In a randomized, non-comparative phase II study, the median PFS among 37 women receiving everolimus pus letrozole was 6.4 months; among 36 patients receiving tamoxifen in combination with medroxyprogesterone on alternate weeks, the median PFS was 3.8 months [51]. A higher RR among chemotherapy-naïve patients compared to the intention-to-treat population is hypothesis-generating and may simply reflect clinicians' preferences to use chemotherapy upfront for women with non-endometrioid EC [51]. Studies investigating other classes of agents targeting the PI3K/AKT/mTOR pathway are underway (NCT02730923. NCT02476955).

It is also notable that PR protein degradation is initiated by MAPK-dependent phosphorylation of ligand-bound PR on S294, and inhibition of the MAPK pathway prevents PR degradation [52]. Interestingly, MAPK phosphorylation of ER enhances its activity [53]. Therefore, treatment with MAPK pathway inhibitors would be expected to increase PR protein expression while decreasing ER activity thus potentially enhancing the efficacy of progesterone-based therapy. Hence, combining a MEK or RAF inhibitor with endocrine therapy warrants further investigation.

3.3. Cell cycle pathways

The combination of a cyclin dependent kinase (CDK) 4/6 inhibitor and letrozole was shown to be effective in breast cancer and was established as a new standard of care with near doubling of PFS with the addition of palbociclib, ribociclib and abemaciclib to an aromatase inhibitor. In breast cancer, pre-clinical data suggested that even tumors that were resistant to endocrine therapy remained dependent on cyclin D1 and CDK4 for cellular proliferation. Extrapolating from the experience in breast and other cancers [54], CDK 4 expression has been reported in 77% endometrioid EC [55]. Furthermore, abnormalities of other cell cycle regulatory proteins occur in EC, including cyclin D1, p16 and the retinoblastoma tumor suppressor (Rb) [55] (Fig. 2).

Tsuda et al. demonstrated that patients with EC had statistically higher expression of CDK4 (34.3%) than those with endometrial hyperplasia (5.6%) or a proliferative endometrium (0%) [55]. In pre-clinical models using EC cell lines HEC-1A and MFE-296 grown subcutaneously in SCID mice, palbociclib resulted in a significant reduction in tumor growth [56]. Given promising pre-clinical and some retrospective cohort data, two studies investigating the use of a CDK4/6 inhibitor plus

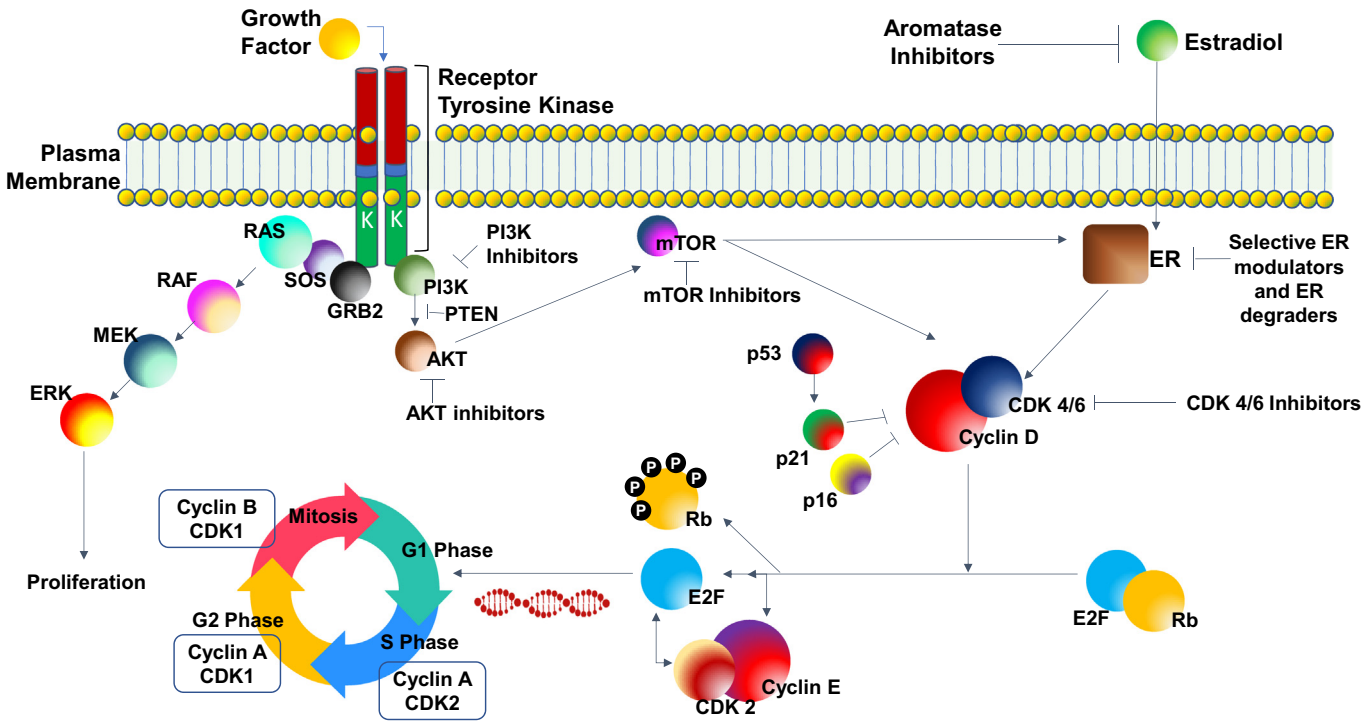

Fig. 2. Signalling pathways contributing to cell proliferation in endometrial cancer and potential strategies to overcome mechanisms of resistance (Adapted from Tripathy et al. [54]). Abbreviations: ER, estrogen receptor; CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin; AKT, protein kinase B; PI3K, phosphatidylinositol 3 kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten; Rb, retinoblastoma; E2F, E2 transcription factor; GRB2, growth factor receptor-bound protein 2; SOS, Son of Sevenless factors; RAS, rat sarcoma viral oncogene homolog; RAF, Rapidly Accelerated Fibrosarcoma kinase; MEK, mitogen activated protein kinase; ERK, extracellular-signal regulated kinases.

letrozole are currently recruiting patients with endometrial cancer (NCT02657928 and NCT02730429).

3.4. Androgens

As illustrated in Fig. 3, the most potent androgen dihydrotestosterone (DHT) demonstrates anti-proliferative effects in EC, which may be partially attributed to reduced ER-induced cell proliferation [57]. Given that expression of AR has been associated with a good prognosis among women with EC [58] and almost 50% of their metastatic lesions express AR [59], it is possible that AR may be a therapeutic target for EC. Specifically, agonists among patients with AR-low or AR negative ECs and/or exogenous administration of androgens among patients with AR-high expressing tumors may serve as novel treatment approaches for women with EC. The anti-proliferative effects of androgens in AR-positive EC cell lines support this hypothesis [60].

3.5. Insulin/metabolic factors

Given that obesity is a risk factor for the development of EC, metabolic pathways have been implicated in progression of ECs. Zhu et al. have shown that insulin-like growth factor 1 receptor (IGF1R) mediates estrogen-driven proliferation in the uterine epithelium, which subsequently results in PI3K pathway activation and the nuclear accumulation of cyclin D1 [61]. In a series of experiments, Zhu et al. further identified that, in addition to the PI3K/mTOR/AKT pathway and IGRF-1, glycogen synthase kinase 3β (GSK3β) may also play a role in mechanism of resistance to endocrine therapy [61] (Fig. 4). GSK3β contributes to the phosphorylation of Thr286, which leads to the nuclear localization of cyclin D, and subsequent activation of the CDK4/6 pathway. In a proof-of-concept experiment, a selective inhibitor of GSK3β, LiCl, reversed progesterone-induced blockade of nuclear cyclin D1 accumulation and thereby inhibited phosphorylation of Rb [62].

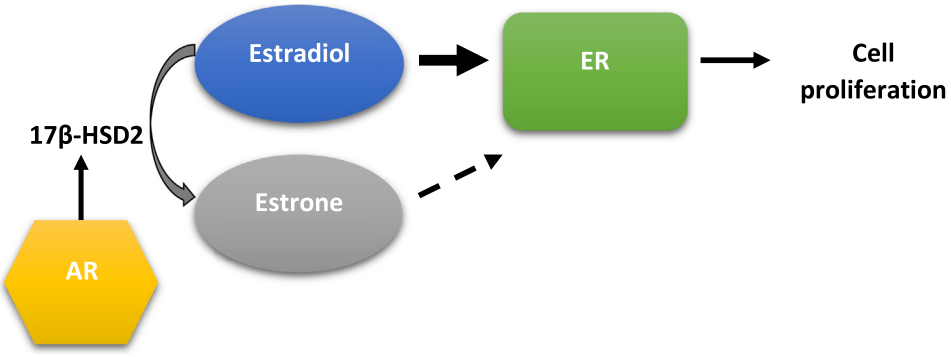

Fig. 3. Estradiol promotes EC proliferation via the estrogen receptor (ER). However, in the presence of the androgen receptor (AR), the 17β-hydroxysteroid dehydrogenase 2 (17β-HSD2) enzyme is upregulated and catalyzes the conversion of estradiol to estrone (a weaker ligand to ER than estradiol), resulting in diminished ER-mediated cell proliferation. (Adapted from Hashimoto et al. [57]).

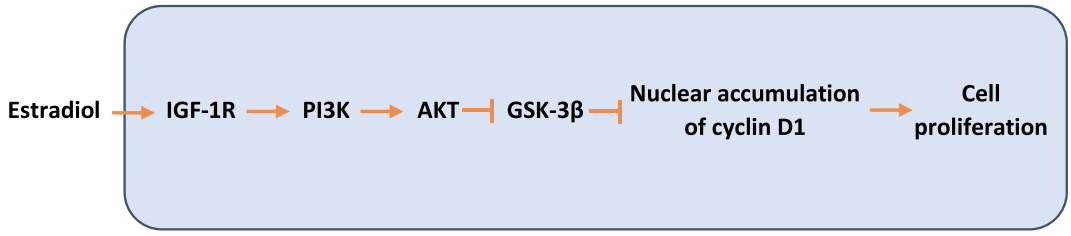

Fig. 4. Estradiol stimulation of uterine epithelial cells ultimately leads to the accumulation of cyclin D1 in the nucleus, with IGF-1R and GSK-3β lying in this linear pathway. (Adapted from Zhu et al. [61]).

Metformin has also been hypothesized as a potential therapeutic agent in EC because pre-clinical work suggests inhibition of proliferation and induction of apoptosis [63]. While metformin's anti-cancer mechanism of action may be attributed to its effects on PTEN/AKT/mTOR (either directly or indirectly), inhibition of MAPK and cyclin D1 expression, as well as reduction in VEGF expression, some data also indicate its ability to influence endocrine therapy in EC [64]. Based on physiologic rationale, retrospective cohort data and pre-clinical evidence, clinical trials investigating the use of metformin in combination with letrozole and everolimus discussed above was designed. As discussed earlier, combining weight loss with metformin and endocrine therapy is being extensively explored for the treatment of early stage low grade cancers and for the treatment of pre-cancerous conditions.

3.6. The immune microenvironment

Tong et al. have recently identified that the microenvironment in EC, specifically the presence of tumor-associated macrophages (TAMs), may contribute to an endocrine resistant phenotype. TAMs were present in higher numbers in EC compared to benign endometrial tissue [65]. Higher histological grade EC had a greater density of TAMs and a reduction in ERα expression compared to low grade tumors [65].

Tung et al. also co-cultured a human acute monocytic leukemia cell line (THP-1) with Ishikawa cells, which are known to express ERα. The "M0" macrophages developed a phenotype similar to TAMs, with dramatic reductions in ESR1 mRNA as well the mRNA of genes encoding PR and cyclin D1 [65]. Reduction in ERα protein expression was confirmed after 72 h of co-culture, with an associated doubling in invasive capacity. Stemming from a human cytokine antibody array, it was ultimately identified that CXCL8 (secreted by TAMs) results in the down-regulation of the HOXB13 transcription factor, which binds the ESR1 promoter and reduces the expression of ERα [65]. Authors also confirmed that the knockdown of HOXB13 resulted in the re-expression of ERα in-vitro, raising the possibility that combining agents targeting TAMs with endocrine therapy may serve as a novel therapeutic strategy. Further work to validate these findings would be of interest.

4. Future directions

Standardization of methodology and cut off points for measurement of ER and PR status in EC is essential to understanding the true prognostic impact these have in EC. The development of additional predictive biomarkers or signatures and a better understanding of ER/PR pathway biology are central to improving responses of women with EC to established endocrine therapies and to designing new therapeutic approaches. In conjunction with ER and PR, genomic tests akin to those utilized in breast cancer could potentially be developed in EC; however, tissue collection in well annotated prospective databases and ideally clinically trials would be required.

In addition to currently investigated CDK4/6 inhibitors, several other strategies have the potential to enhance the response of women with EC to endocrine therapy. The potential combination of endocrine therapy with PI3K inhibitors, MAPK inhibitors or epigenetic modifiers warrants investigation, particularly given established agents that have shown benefit in other disease settings. Emerging agents that modulate TAMs and CDK2 inhibitors may also hold promise, although pre-clinical data specific to EC is currently lacking for the latter.

Finally, in addition to enhancing responses of women to endocrine therapy for advanced EC, efforts to *prevent* metastatic recurrences are also required. Efforts to modulate risk factors for recurrent disease and/or preventative therapeutic strategies (i.e. adjuvant endocrine therapy) warrant further investigation.

Conflict of interest statement

K.J.J. has served as a consultant for and/or attended advisory boards for Esai, Genomic Health Inc., Novartis, Purdue Pharma and Roche; she has also received research support from Astra Zeneca. L.D. has served on the medical advisory board for Merck, Genentech, MedImmune and she is a member of the data safety monitoring board (DSMB) for Inovio. H.J.M. reports no conflicts of interest.

Author contributions

All authors contributed to the conception of this work and contributed to writing/editing of the manuscript.

Acknowledgements

The authors would like to thank Dr. William Tran for his help in designing the figures in this manuscript.

References

[1] Surveillance, Epidemiology and End Results Program, https://seer.cancer.gov/statfacts/html/corp.html, Accessed date: 6 November 2018.
[2] L. Rahib, B.D. Smith, R. Aizenberg, A.B. Rosenzweig, J.M. Fleshman, L.M. Matrisian, Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States, Cancer Res. 74 (11) (2014) 2913–2921.
[3] J.N. McAlpine, S.M. Temkin, H.J. Mackay, Endometrial cancer: not your grandmother's cancer, Cancer 122 (18) (2016) 2787–2798.
[4] P. Morice, A. Leary, C. Creutzberg, N. Abu-Rustum, E. Darai, Endometrial cancer, Lancet 387 (10023) (2016) 1094–1108.
[5] C. Kandoth, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, H. Shen, et al., Integrated genomic characterization of endometrial carcinoma, Nature 497 (7447) (2013) 67–73.
[6] H.J. MacKay, D.A. Levine, V.L. Bae-Jump, D.W. Bell, J.N. McAlpine, A. Santin, et al., Moving forward with actionable therapeutic targets and opportunities in endometrial cancer: NCI clinical trials planning meeting report on identifying key genes and molecular pathways for targeted endometrial cancer trials, Oncotarget 8 (48) (2017) 84579–84594.
[7] P.A. Ott, Y.J. Bang, D. Berton-Rigaud, E. Elez, M.J. Pishvaian, H.S. Rugo, 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. 35 (22) (2017) 2535–2541.
[8] A.N. Karnezis, S. Leung, J. Magrill, M.K. McConechy, W. Yang, C. Chow, et al., Evaluation of endometrial carcinoma prognostic immunohistochemistry markers in the context of molecular classification, J. Pathol. Clin. Res. 3 (4) (2017) 279–293.
[9] P.P. Martin-Hirsch, A. Bryant, S.L. Keep, H.C. Kitchener, R. Lilford, Adjuvant progestagens for endometrial cancer, Cochrane Database Syst. Rev. 6 (2011), CD001040. .
[10] D.G. Anderson, Management of advanced endometrial adenocarcinoma with medroxyprogesterone acetate, Am. J. Obstet. Gynecol. 92 (1965) 87–99.
[11] F. Kokka, E. Brockbank, D. Oram, C. Gallagher, A. Bryant, Hormonal therapy in advanced or recurrent endometrial cancer, Cochrane Database Syst. Rev. 12 (2010), CD007926. .
[12] W.J. Koh, N.R. Abu-Rustum, S. Bean, K. Bradley, S.M. Campos, K.R. Cho, et al., Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. 16 (2) (2018) 170–199.

[13] J.L. Ethier, D.N. Desautels, E. Amir, H. MacKay, Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis, Gynecol. Oncol. 147 (1) (2017) 158–166.
[14] C.W. Whitney, V.L. Brunetto, R.J. Zaino, S.S. Lentz, J. Sorosky, D.K. Armstrong, et al., Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study, Gynecol. Oncol. 92 (1) (2004) 4–9.
[15] J.T. Thigpen, M.F. Brady, R.D. Alvarez, M.D. Adelson, H.D. Homesley, A. Manetta, et al., Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group, J. Clin. Oncol. 17 (6) (1999) 1736–1744.
[16] R.J. Zaino, W.E. Brady, W. Todd, K. Leslie, E.G. Fischer, N.S. Horowitz, et al., Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a Gynecologic Oncology Group study, Int. J. Gynecol. Pathol. 33 (6) (2014) 543–553.
[17] W.D. Baker, S.R. Pierce, A.M. Mills, P.A. Gehrig, L.R. Duska, Nonoperative management of atypical endometrial hyperplasia and grade 1 endometrial cancer with the levonorgestrel intrauterine device in medically ill post-menopausal women, Gynecol. Oncol. 146 (1) (2017) 34–38.
[18] A. Thangavelu, M.J. Hewitt, N.D. Quinton, S.R. Duffy, Neoadjuvant treatment of endometrial cancer using anastrozole: a randomised pilot study, Gynecol. Oncol. 131 (3) (2013) 613–618.
[19] L. Berstein, S. Maximov, E. Gershfeld, I. Meshkova, V. Gamajunova, E. Tsyrlina, et al., Neoadjuvant therapy of endometrial cancer with the aromatase inhibitor letrozole: endocrine and clinical effects, Eur. J. Obstet. Gynecol. Reprod. Biol. 105 (2) (2002) 161–165.
[20] A. Bonaventura, R.L. O'Connell, C. Mapagu, P.J. Beale, O.M. McNally, L.R. Mileshkin, et al., Paragon (ANZGOG-0903): phase 2 study of anastrozole in women with estrogen or progesterone receptor-positive platinum-resistant or -refractory recurrent ovarian Cancer, Int. J. Gynecol. Cancer 27 (5) (2017) 900–906.
[21] L.R. Mileshkin, R.J. Edmondson, R. O'Connell, K.M. Sjoquist, D. Cannan, R. Jyothirmayi, et al., Phase II study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: the PARAGON trial-ANZGOG 0903, J. Clin. Oncol. 34 (15_supply) (2016) 5520.
[22] P.R. Manna, D. Molehin, A.U. Ahmed, Dysregulation of aromatase in breast, endometrial, and ovarian cancers: an overview of therapeutic strategies, Prog. Mol. Biol. Transl. Sci. 144 (2016) 487–537.
[23] P. Pautier, I. Vergote, F. Joly, B. Melichar, E. Kutarska, G. Hall, et al., A phase 2, randomized, open-label study of irosustat versus megestrol acetate in advanced endometrial cancer, Int. J. Gynecol. Cancer 27 (2) (2017) 258–266.
[24] I.D. Gallos, J. Yap, M. Rajkhowa, D.M. Luesley, A. Coomarasamy, J.K. Gupta, Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 207 (4) (2012) 266.e1–266.e12.
[25] C.C. Gunderson, A.N. Fader, K.A. Carson, R.E. Bristow, Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review, Gynecol. Oncol. 125 (2) (2012) 477–482.
[26] Z.R. Greenwald, L.N. Huang, M.D. Wissing, E.L. Franco, W.H. Gotlieb, Does hormonal therapy for fertility preservation affect the survival of young women with early-stage endometrial cancer? Cancer 123 (9) (2017) 1545–1554.
[27] M.L. MacKintosh, A.E. Derbyshire, R.J. McVey, J. Bolton, M. Nickkho-Amiry, C.L. Higgins, et al., The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk, Int. J. Cancer 144 (3) (2019 Feb 1) 641–650.
[28] A.L. Hawkes, M. Quinn, V. Gebski, J. Armes, D. Brennan, M. Janda, et al., Improving treatment for obese women with early stage cancer of the uterus: rationale and design of the levonorgestrel intrauterine device ± metformin ± weight loss in endometrial cancer (feMME) trial, Contemp. Clin. Trials 39 (1) (2014) 14–21.
[29] A. Talhouk, M.K. McConechy, S. Leung, W. Yang, A. Lum, J. Senz, et al., Confirmation of ProMisE: a simple, genomics-based clinical classifier for endometrial cancer, Cancer 123 (5) (2017) 802–813.
[30] L.R. Duska, D.H. Suh, M. Wilson, Diane S. Yamada, International Gynecologic Cancer Society (IGCS) 2018: Meeting report, Gynecol. Oncol. (2018 Oct 28)https://doi.org/10.1016/j.ygyno.2018.10.020 (epub ahead of print).
[31] Y. Zhang, D. Zhao, C. Gong, F. Zhang, J. He, W. Zhang, et al., Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta-analysis, World J. Surg. Oncol. 13 (2015) 208.
[32] J. Trovik, E. Wik, H.M. Werner, C. Krakstad, H. Helland, I. Vandenput, et al., Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial, Eur. J. Cancer 49 (16) (2013) 3431–3441.
[33] B. Patel, S. Elguero, S. Thakore, W. Dahoud, M. Bedaiwy, S. Mesiano, Role of nuclear progesterone receptor isoforms in uterine pathophysiology, Hum. Reprod. Update 21 (2) (2015) 155–173.
[34] V. Fabris, M.F. Abascal, S. Giulianelli, M. May, G.R. Sequeira, B. Jacobsen, et al., Isoform specificity of progesterone receptor antibodies, J. Pathol. Clin. Res. 3 (4) (2017) 227–233.
[35] M.K. Kowalik, R. Rekawiecki, J. Kotwica, The putative roles of nuclear and membrane-bound progesterone receptors in the female reproductive tract, Reprod. Biol. 13 (4) (2013) 279–289.
[36] D. Garg, S.S.M. Ng, K.M. Baig, P. Driggers, J. Segars, Progesterone-mediated non-classical signaling, Trends Endocrinol. Metab. 28 (9) (2017) 656–668.
[37] E. Baxter, K. Windloch, G. Kelly, J.S. Lee, F. Gannon, D. Brennan, Molecular basis of distinct oestrogen responses in endometrial and breast cancer, Endocr. Relat. Cancer 26 (1) (2019 Jan 1) 31–46.
[38] F. Holst, E.A. Hoivik, W.J. Gibson, A. Taylor-Weiner, S.E. Schumacher, Y.W. Asmann, et al., Recurrent hormone-binding domain truncated ESR1 amplifications in primary endometrial cancers suggest their implication in hormone independent growth, Sci. Rep. 6 (2016) 25521.
[39] D.S. Tan, M.B. Lambros, C. Marchiò, J.S. Reis-Filho, ESR1 amplification in endometrial carcinomas: hope or hyperbole? J. Pathol. 216 (3) (2008) 271–274.
[40] E. Stelloo, R.A. Nout, E.M. Osse, I.J. Jürgenliemk-Schulz, J.J. Jobsen, L.C. Lutgens, et al., Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts, Clin. Cancer Res. 22 (16) (2016) 4215–4224.
[41] B. Oronsky, N. Oronsky, S. Knox, G. Fanger, J. Scicinski, Episensitization: therapeutic tumor resensitization by epigenetic agents: a review and reassessment, Anti Cancer Agents Med. Chem. 14 (8) (2014) 1121–1127.
[42] S. Yang, X. Xiao, Y. Jia, X. Liu, Y. Zhang, X. Wang, et al., Epigenetic modification restores functional PR expression in endometrial cancer cells, Curr. Pharm. Des. 20 (11) (2014) 1874–1880.
[43] M. Sasaki, M. Kaneuchi, S. Fujimoto, Y. Tanaka, R. Dahiya, Hypermethylation can selectively silence multiple promoters of steroid receptors in cancers, Mol. Cell. Endocrinol. 202 (1–2) (2003) 201–207.
[44] K. Ihira, P. Dong, Y. Xiong, H. Watari, Y. Konno, S.J. Hanley, et al., EZH2 inhibition suppresses endometrial cancer progression via miR-361/Twist axis, Oncotarget 8 (8) (2017) 13509–13520.
[45] G. Zhang, Y. Cheng, Q. Zhang, X. Li, J. Zhou, J. Wang, et al., ATX-LPA axis facilitates estrogen-induced endometrial cancer cell proliferation via MAPK/ERK signaling pathway, Mol. Med. Rep. 17 (3) (2018) 4245–4252.
[46] L. Zhou, B. Cai, W. Bao, Y.Y. He, X.Y. Chen, Y.X. Yang, et al., Crosstalk between estrogen receptor and mitogen-activated protein kinase signaling in the development and progression of endometrial cancer, Int. J. Gynecol. Cancer 21 (8) (2011) 1357–1365.
[47] B.M. Slomovitz, Y. Jiang, M.S. Yates, P.T. Soliman, T. Johnston, M. Nowakowski, et al., Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma, J. Clin. Oncol. 33 (8) (2015) 930–936.
[48] H.J. Mackay, E.A. Eisenhauer, S. Kamel-Reid, M. Tsao, B. Clarke, K. Karakasis, et al., Molecular determinants of outcome with mammalian target of rapamycin inhibition in endometrial cancer, Cancer 120 (4) (2014) 603–610.
[49] P.T. Soliman, S.N. Westin, D.A. Iglesias, M.F. Munsell, B.M. Slomovitz, K.H. Lu, et al., Phase II study of everolimus, letrozole, and metformin in women with advanced/recurrent endometrial cancer, J. Clin. Oncol. 34 (15_suppl) (2016) 5506.
[50] G.F. Fleming, V.L. Filiaci, B. Marzullo, R.J. Zaino, S.A. Davidson, M. Pearl, et al., Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study, Gynecol. Oncol. 132 (3) (2014) 585–592.
[51] B. Slomovitz, et al., GOG 3007, a Randomized Phase II Trial of Everolimus and Letrozole or Hormonal Therapy (Medroxyprogesterone/Tamoxifen) in Women With Advanced, Persistent, or Recurrent Endometrial Carcinoma: A GOG Foundation Study, SGO, 2018 (Abstract 1).
[52] C.A. Lange, T. Shen, K.B. Horwitz, Phosphorylation of human progesterone receptors at serine-294 by mitogen-activated protein kinase signals their degradation by the 26S proteasome, Proc. Natl. Acad. Sci. U. S. A. 97 (3) (2000) 1032–1037.
[53] S. Kato, H. Endoh, Y. Masuhiro, T. Kitamoto, S. Uchiyama, H. Sasaki, et al., Activation of the estrogen receptor through phosphorylation by mitogen-activated protein kinase, Science 270 (5241) (1995) 1491–1494.
[54] D. Tripathy, A. Bardia, W.R. Sellers, Ribociclib (LEE011): mechanism of action and clinical impact of this selective cyclin-dependent kinase 4/6 inhibitor in various solid tumors, Clin. Cancer Res. 23 (13) (2017) 3251–3262.
[55] H. Tsuda, K. Yamamoto, T. Inoue, I. Uchiyama, N. Umesaki, The role of p16-cyclin d/CDK-pRb pathway in the tumorigenesis of endometrioid-type endometrial carcinoma, Br. J. Cancer 82 (3) (2000) 675–682.
[56] M.A. Dosil, C. Mirantes, N. Eritja, I. Felip, R. Navaridas, S. Gatius, et al., Palbociclib has antitumour effects on Pten-deficient endometrial neoplasias, J. Pathol. 242 (2) (2017) 152–164.
[57] C. Hashimoto, Y. Miki, S. Tanaka, K. Takagi, M. Fue, D. Zhulanquqige, et al., 17β-Hydroxysteroid dehydrogenase type 2 expression is induced by androgen signaling in endometrial cancer, Int. J. Mol. Sci. 19 (4) (2018) 1139.
[58] A.M. Kamal, J.N. Bulmer, S.B. DeCruze, H.F. Stringfellow, P. Martin-Hirsch, D.K. Hapangama, Androgen receptors are acquired by healthy postmenopausal endometrial epithelium and their subsequent loss in endometrial cancer is associated with poor survival, Br. J. Cancer 114 (2016) 688–696.
[59] I.L. Tangen, T.B. Onyango, R. Kopperud, A. Berg, M.K. Halle, A.M. Øyan, et al., Androgen receptor as potential therapeutic target in metastatic endometrial cancer, Oncotarget 7 (31) (2016) 49289–49298.
[60] R. Hackenberg, K.D. Schultz, Androgen receptor mediated growth control of breast cancer and endometrial cancer modulated by antiandrogen- and androgen-like steroids, J. Steroid Biochem. Mol. Biol. 56 (1–6 Spec) (1996) 113–117.
[61] L. Zhu, J.W. Pollard, Estradiol-17B regulated mouse uterine epithelial cell proliferation through insulin-like growth factor1 signalling, PNAS 104 (40) (2007) 15847–15851.
[62] B. Chen, H. Pan, L. Zhu, Y. Deng, J.W. Pollard, Progesterone inhibits the estrogen-induced phosphoinositide 3-kinase → AKT → GSK-3beta → cyclin D1 → pRB pathway to block uterine epithelial cell proliferation, Mol. Endocrinol. 19 (8) (2005) 1878–1890.
[63] K.M. Schuler, B.S. Rambally, M.J. DiFurio, B.P. Sampey, P.A. Gehrig, L. Makowski, et al., Antiproliferative and metabolic effects of metformin in a preoperative window clinical trial for endometrial cancer, Cancer Med. 4 (2) (2015) 161–173.
[64] L.A. Cantrell, C. Zhou, A. Mendivil, K.M. Malloy, P.A. Gehrig, V.L. Bae-Jump, Metformin is a potent inhibitor of endometrial cancer cell proliferation – implications for a novel treatment strategy, Gynecol. Oncol. 116 (1) (2010) 92–98.
[65] H. Tong, J.Q. Ke, F.Z. Jiang, X.J. Wang, F.Y. Wang, Y.R. Li, et al., Tumor-associated macrophage-derived CXCL8 could induce ERα suppression via HOXB13 in endometrial cancer, Cancer Lett. 376 (1) (2016) 127–136.