



# **Molecular Aspects of Cancer Research Endometrium – The Prospect of Personalized Treatment**

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## **Author's contribution**

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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## **ABSTRACT**

**Aims:** Endometrial cancer is the most common gynaecological cancer, and there is a growing interest in identifying the molecular pathways involved and developing molecular-targeted treatment to prevent it. Present study was aimed to give an overview of the molecular processes involved in endometrial cancer development and treatment options.

**Methods:** We conducted a comprehensive systematic literature review and meta-analysis. For that purpose, PubMed database was searched for related studies till June 2021 and a through selection process was adopted to select the eligible studies.

**Results:** Endometrial malignancies are complicated molecularly, and their focused therapy has a wide range of outcomes, with median progressive survival rates ranging from 2.3 to 18 months.

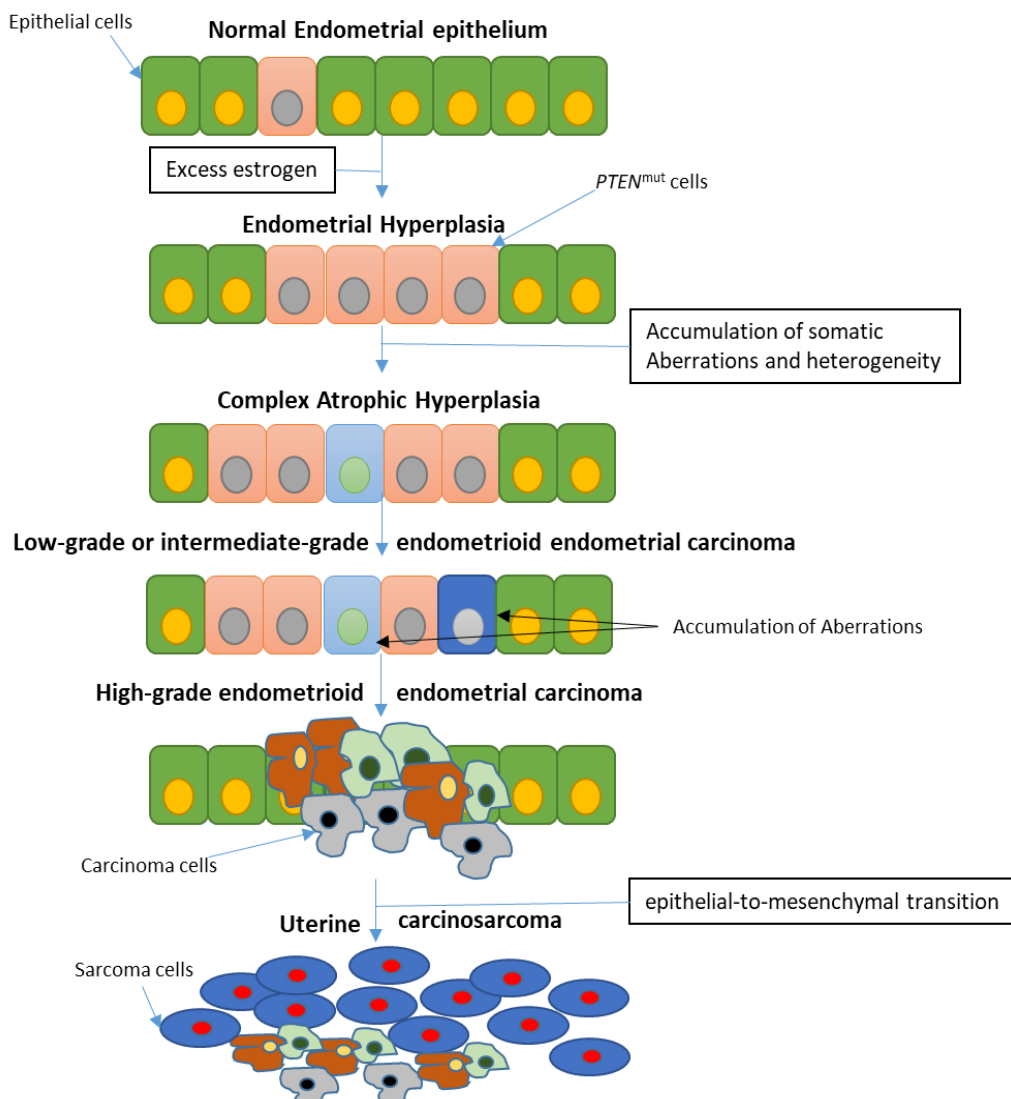
**Conclusions:** The effective treatment and therapy need a detailed understanding of the molecular mechanisms underlying the creation and progression of endometrial cancer, as well as the development of innovative targeted therapeutic agents.

*Keywords: Endometrium cancer; molecular mechanism; treatment; meta-analysis.*

## 1. INTRODUCTION

In the United States, endometrial cancer is the most prevalent gynecologic or uterine cancer, with an increasing incidence and disease-related death [1]. Despite the fact that endometrial cancer in its early stages is associated with a higher 5-year relative survival rate (96%). While it is most often diagnosed malignancy in postmenopausal women, premenopausal women account for 14% of cases, with 5% of cases occurring in women under the age of 40. The average age of diagnosis in the United States is 62 years [2]. Uterine cancer is identified in the majority of women with endometrial cancer (67%) at an early stage. Age, metabolic condition, race, genetic predispositions, and

unrestricted estrogen exposure are all important risk factors for endometrial cancer. Approximately 90% of endometrial cancer occurrences are spontaneous, with the remaining 10% being inherited. In response to fluctuations in estrogen and progesterone during the menstrual cycle, the endometrium experiences structural alterations and changes in specialized cells. Endometrial cancer is closely linked to epidemiological risk factors that result in an excess of estrogen compared to progesterone. Endometrial hyperplasia can develop as a result of unopposed estrogen stimulation of the uterine epithelium, which can progress to complicate a typical hyperplasia and endometrial cancer (Fig. 1).



**Fig. 1. Endometrioid endometrial cancers begin and develop from normal endometrial epithelium, according to a diagram adapted from Urick and Bell [3]**

Endometrial cancer has traditionally been categorized into two broad classifications: type I and type II. Type I cancers account for the majority of diagnoses and have an overall 5-year survival rate of 85% as well as very low recurrence rates (20%). Type I malignancies typically have a good prognosis since they are low-grade and often limited to the uterus at the time of diagnosis. Situations that enhance estrogen exposure from both endogenous and exogenous sources have been related to type I tumors. They're well-differentiated, seem more like normal tissue, and have a good prognosis [4]. Type II cancers, on the other hand, are a less frequent type of cancer, accounting for 10-20% of endometrial cancers, including serous carcinomas (10%) and clear cell carcinomas (5%). Type II malignancies are aggressive, often appearing late in life, and have a poor prognosis, with a high rate of recurrence (about 50%) and a lower 5-year overall survival rate (55%). Type I and type II endometrial cancers are differentiated by genetic changes in addition to their morphologic and clinical characteristics. Endometrial cancers are marked by a number of genetic changes, the most common of which is a mutation in the *PTEN* gene. Several tumor suppressor genes have been linked to the development of endometrial malignancies. There is evidence that the phosphatidylinositol-3

kinase/Phosphatase and tensin homolog/Akt kinase (PI3K/PTEN/AKT) pathway is the most frequently altered molecular pathway in type I endometrial carcinomas, which is dysregulated by oncogenic mutations, PTEN loss of function, and/or overexpression of upstream tyrosine kinase growth factor receptor leading to uncontrolled cell proliferation and survival. The tumor suppressors p53 and/or p16, which induce cell cycle dysregulation and genetic instability, are the primary pathway changes in type II endometrial malignancies, and there were higher levels of mammalian target of rapamycin (mTOR) or tumor protein 53 (TP53) mutations in serous carcinomas [5]. Microsatellite instability (MSI) and specific mutations of the K-ras and -catenin genes are also seen in endometrioid endometrial malignancies. In type I endometrial cancer, inactivation of MutL protein homolog 1 (MLH1), a component of the mismatch repair mechanism, is a typical occurrence. Hypermethylation of CpG islands in the gene promoter causes this change, which is known as epigenetic silencing. Inactivation of p16 and overexpression of human epidermal growth factor receptor 2 (HER-2/neu) are also common genetic changes in type II endometrial malignancies. Endometrial malignancies have a variety of molecular pathways, as showed in Fig. 2.

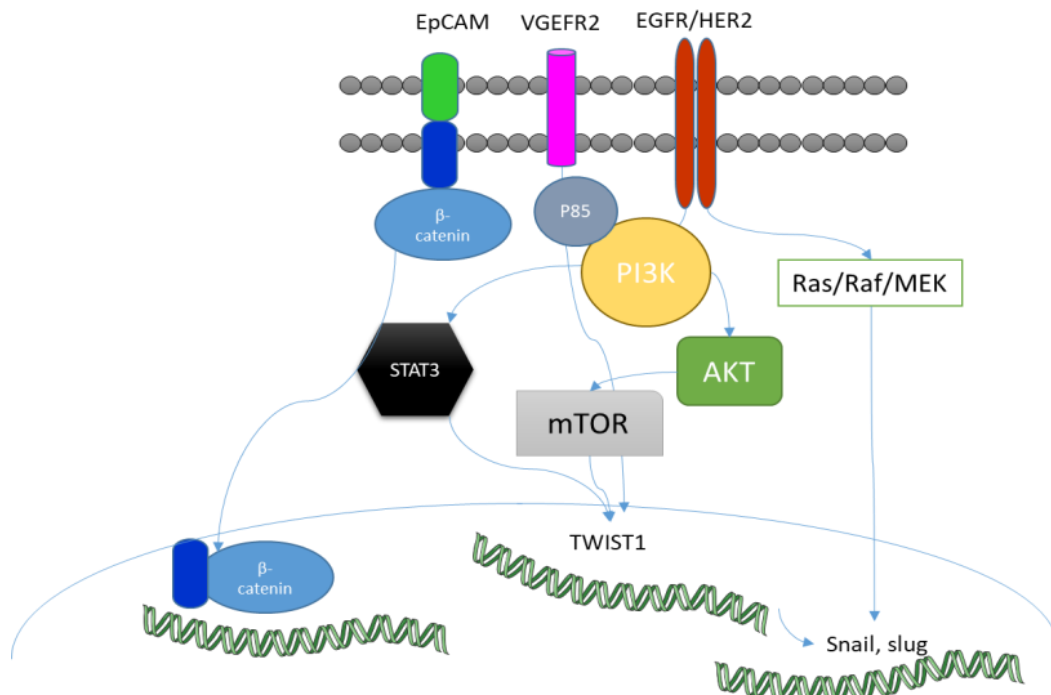


Fig. 2. Molecular mechanisms for endometrial cancer adapted from Dong et al. and Dedes et al. [5,6]

Surgical treatment for endometrial cancer patients, including total hysterectomy, removal of residual adnexal structures, and proper surgical staging in patients at risk for extra-uterine illness, is the cornerstone of curative therapy. The standard treatment for endometrial cancer is surgery, with platinum-based chemotherapy or radiotherapy recommended as adjuvant therapy if patients have some risk factors for recurrence, such as a high histologic grade or high-risk histology, spread to the uterine adnexae, or lymph node metastasis. The development of treatment for advanced or recurring endometrial cancer, on the other hand, has been insufficient, and the prognosis has not improved. The development of molecular-targeted therapy as a new therapeutic method for human malignancies has been aided by recent advances in molecular biology research.

were used in the search. We also looked through the reference lists of papers found during the initial search to see if there were any other studies that were relevant. Authors independently vetted titles and abstracts for inclusion. Fig. 3 depicts the search technique as well as the selection criteria.

The inclusion and exclusion criteria applied to select studies for the meta-analysis as showed in Table 1. Author name, year, drug/therapeutic agent, trial phase, median progression and medial overall survival rate, number of patients enrolled in each study, mean age of the study participants, and drugs molecular target were retrieved.

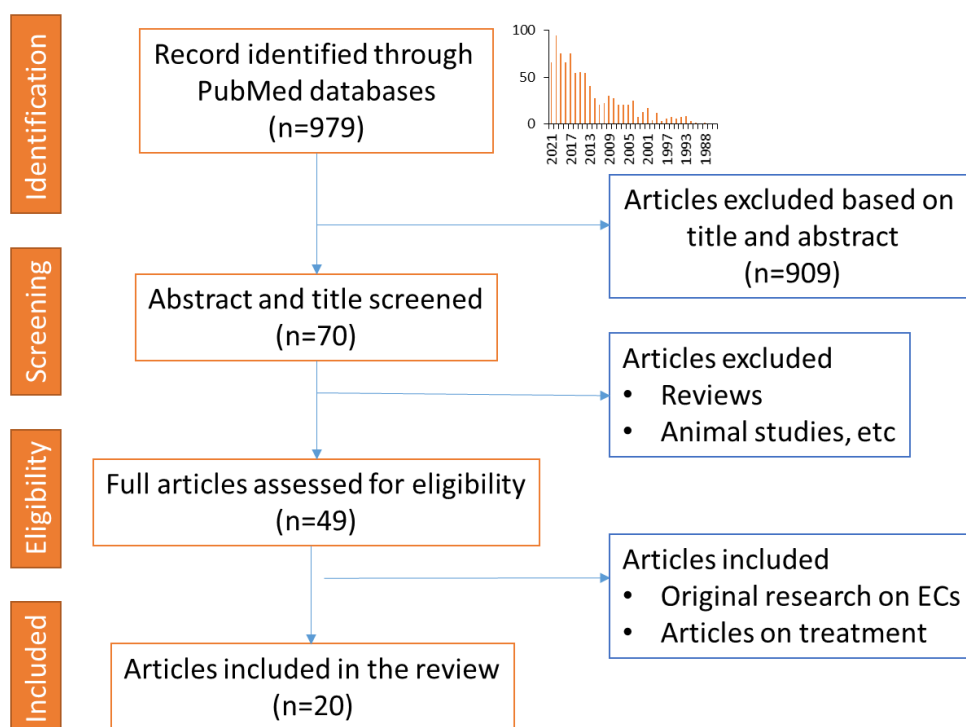
**Table 1. Criteria for the inclusion and exclusion of studies in the meta-analysis**

Inclusion	Exclusion
Endometrial cancer	Other cancer types
Treatment related studies	Non-treatment studies
Human studies	Animal models
Written in English	Not written in English
Original research	Literature review

## 2. MATERIAL AND METHODS

### 2.1 Study Selection and Data Extraction

Detailed In June 2021, we conducted a search for this systematic review and meta-analysis. We included research on endometrial cancer molecular pathways and treatment outcomes. The terms molecular mechanisms, endometrial cancer, uterine cancer, treatment, and therapy



**Fig. 3. Flow chart diagram for study reports**

**Table 2. Studies presenting drugs targeting molecular mechanisms of endometrial cancers and their median progression free survival and median overall survival\***

Author (Year)	Drug/ Therapeutic agent	Phase of study	Median Progression free survival	Median overall survival	No. of patients enrolled in study	Mean age (Range)	Molecular Target
Makker et al. [7]	Lenvatinib Plus Pembrolizumab	Phase Ib/II	7.4	16.7	108	65.3	VEGF and FGF
Lorusso et al. [8]	Carboplatin-paclitaxel vs Carboplatin-Paclitaxel- Bevacizumab	Phase II	0.5 vs 13.7	29.7 vs 40.0	108	65 (32-80) vs 63 (28-81)	VEGF
Heudel et al. [9]	BKM120 (buparlisib)	Phase II	4.5 months (CI 2.8-6.1)	NR	40 (24 @ 60 mg and 16 @ 100 mg)	67.1 (50.0- 79.7) @ 60 mg, 65.2 (53.6- 79.5) @ 100 mg	PI3K
Makker et al. [10]	Apitolisib	Phase II	3.5 (CI 2.7-3.7)	15.7	56	65.5 (30-81)	PI3K/mTOR
Bender et al. [11]	Cediranib	Phase II	3.65	12.5	53	65.5	tyrosine kinase
Coleman et al. [12]	Selumetinib	Phase II	2.3	8.5	54	62 (40-80)	MEK-1/2
Simpkinset al. [13]	Paclitaxel, carboplatin, and bevacizumab	Phase II	18 month	58 month	15	63 (32-88)	VEGF
Slomovitz et al. [14]	Everolimus and Letrozole	Phase II	NR	NR	38	62 (24-82)	PI3K
Fleming et al. [15]	Temsirolimus with or without megestrol acetate and tamoxifen	Phase II	4.9	10.8	71	40-80	mTOR
Matulonis et al. [16]	Pilaralisib	Phase II	> 183 days	NR	67	64 (46-89)	PI3K
Powell et al. [17]	Brivanib	Phase II	3.3	10.7	45	64 (40-89)	VEGF

Author (Year)	Drug/ Therapeutic agent	Phase of study	Median Progression free survival	Median overall survival	No. of patients enrolled in study	Mean age (Range)	Molecular Target
Tsoref et al. [18]	Ridaforolimus	Phase II	NR	NR	34	63 (43-89)	mTOR
Viswanathan et al. [19]	Radiation and concurrent bevacizumab	Phase II	NR	NR	19	62 (46–85)	VEGF
Castonguay et al. [20]	Sunitinib	Phase II	3.5 (CI 2.5-5.3)	19.4	34	65 (41-83)	tyrosine kinase
Alvarez et al. [21]	Bevacizumab and temsirolimus	Phase II	5.6	16.9	53	63 (30-89)	anti-angiogenic and mTOR pathway
Leslie et al. [22]	Lapatinib	Phase II	NR	NR	31	NR	first dual inhibitor of EGFR and HER2
Oza et al. [23]	Temsirolimus	Phase II	3.25		62	66 (52-80)	PTEN
Aghajanian et al. [24]	Bevacizumab	Phase II	4.2	10.5	56	62 (32-84)	VEGF

\* NR = not reached

### 3. RESULTS AND DISCUSSION

A total of 979 studies record was identified using PubMed database search based on various keywords related to molecular mechanisms, endometrial cancer, uterine cancer, treatment and therapy. From all studies 909 studies were excluded based on their abstract and titles. However, from 70 screened studies, 48 studies fulfil the eligibility criteria. Upon further through investigation only 21 studies were elaborated in this meta-analysis. From selected studies most of the studies were from phase II whereas on study follow phase Ib/II criteria. The data extracted from those studies have been presented in Table 2. Most of the drugs used in these studies target various molecular mechanisms in as showed in Table 2 but their Median progression free survival and median overall survival rates vary among different age groups and Therapeutic agents. A total of 1013 patients enrolled in these studies with mean age of > 60.

Endometrial cancer is one of the most prevalent malignancies among women worldwide, with an increasing incidence and death rate in the United States [1]. Postmenopausal women, on average 60 years old when diagnosed, are the majority of those affected by this malignancy. Between the ages of 75 and 79, the largest prevalence occurs, with 85% of cases occurring after the age of 50 and only 5% occurring before the age of 40. These facts were also discovered through our meta-analysis as a total of 1049 patients enrolled in all included studies with mean age of > 60. Fig. 2 depicts some essential biological pathways involved in endometrial cancer development. All endometrial malignancies should be screened for DNA mismatch repair gene mutations, according to experts [25]. The majority of endometrial cancer patients require surgery, which involves hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Patients with unresectable illness or significant medical comorbidities may get nonsurgical treatment in the form of primary radiation with or without chemotherapy, or chemotherapy alone. Hormonal therapy might potentially be used to treat people who are medically inoperable but dont want surgery, radiation, or cytotoxic chemotherapy. Hormonal therapy may be an option for a small group of premenopausal women who dont want to have children; however, it is not considered standard of care, and these women should be properly counselled before choosing conservative

treatment [25]. Other possibilities include tamoxifen, luteinizing hormone-releasing hormone agonists, fulvestrant, and aromatase inhibitors. Hormonal treatment may be helpful for certain women with type 1 benign endometrial cancer who do not desire to have children [26]. Medroxyprogesterone acetate, megestrol acetate, or a levonorgestrel-containing intrauterine device are all options for continuous progestin therapy [27]. Chemotherapy also has a role in unresectable metastatic cancer, surgically resected advanced disease, and recurrent sickness, although endometrial malignancies are often chemotherapy-insensitive tumors that respond better to radiotherapy. Although the function of chemotherapy in high-risk, early-stage cancer is still being researched, multimodality therapy is presently recommended for type II histology, which is more aggressive and has a higher prevalence of extrauterine disease. Adjuvant therapy is used to minimize the chance of disease recurrence in newly diagnosed endometrial cancer. Few studies have described the use of adjuvant treatment for endometrial cancer in our review. According to the surgery stage, tumor histology, and adverse risk factors, adjuvant treatment is suggested. Advanced age, lymph vascular invasion, tumor size, tumor grade, and involvement of the lower uterine segment or the surface cervical glands are all risk factors. Adjuvant therapy is recommended more frequently when tumor grade, myometrial invasion, and cervical involvement deteriorate, because the risk of relapse increases. They have a high-risk histology. Endometrial tumors of type II are never categorized as low- or intermediate-risk, and are always classified as high-risk. Radiation, which can be delivered by external beam radiotherapy or vaginal brachytherapy, is the most frequent adjuvant treatment for endometrial cancer. In medically inoperable patients, radiotherapy can be used as an adjuvant treatment, as well as for definitive treatment, local recurrence, and palliative care. As described by Viswanathan, Lee [19] in our meta-analysis study. Vaginal brachytherapy, on the other hand, is designed to deliver the dosage directly to the vaginal surface and any underlying lymphatic pathways, and thus has a low morbidity rate. In the preoperative setting, patients would get vaginal brachytherapy with or without external beam radiation, followed by hysterectomy, before surgical staging. As a result of surgical staging, the utilization of radiation for type I endometrial treatment has reduced [25]. Patients with no residual disease in the hysterectomy specimen and low-grade

endometrioid endometrial cancer confined to the inner half of the endometrium and otherwise low risk may opt out of radiation after surgical staging because it has not been proven to provide any additional benefit [28]. The National Comprehensive Cancer Network also now recommends adjuvant chemotherapy for stages IB through IV. Women with high-risk stage IA cancer may be given chemotherapy. Multiagent chemotherapy regimens such as carboplatin/paclitaxel, carboplatin/docetaxel, cisplatin/doxorubicin/paclitaxel, cisplatin/doxorubicin, or carboplatin/paclitaxel/bevacizumab are all suggested [25]. It has also been described in our analysis (Table 2). A combination of everolimus and letrozole is currently being explored, with promising results for endometrioid histology as showed in Table 2.15 Carboplatin with paclitaxel is a superior choice for advanced/metastatic or recurrent endometrial cancer because of its comparable response rates and reduced toxicity.<sup>30</sup> Carboplatin/paclitaxel has a response rate of 40 to 62% in this situation, with overall survival ranging from 13 to 29 months. Carboplatin/paclitaxel is the favored regimen for most patients since it is generally better tolerated than other medicines [29]. If paclitaxel is rival indicated, docetaxel could be used instead.<sup>31</sup> If multiagent chemotherapy regimens are not tolerated or are contraindicated, single-agent therapeutic approaches may be investigated [27]. Paclitaxel, albumin-bound paclitaxel, cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, topotecan, and docetaxel are some of the choices [25]. The recommended first-line treatment for advanced, recurring, and metastatic endometrial cancer is paclitaxel plus carboplatin [29]. Only two additional medicines were expressly approved in the metastatic situation [31]. Regardless of platinum use, megestrol acetate is approved for the palliative treatment of advanced endometrial cancer. Pembrolizumab is a monoclonal antibody that targets the programmed death receptor-1 (PD-1) and has been approved for solid tumors with microsatellite instability-high (MSI-H)/mismatch-repair-deficient (dMMR) that have progressed after prior therapy and have no other treatment alternatives.<sup>8</sup> Pembrolizumab is used to treat metastatic MSI-H endometrial cancer following failure of first-line treatment [7]. Phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) inhibitors, angiogenesis inhibitors, epidermal growth factor receptors (EGFR) inhibitors, mitogen-activated protein kinase (MAP-K) inhibitors, and antibodies against the human

epidermal growth factor receptor (HER)2/neu have all been investigated [32,33]. Clinical trials have yielded inconsistent outcomes, resulting in restricted recommendations for these drugs. The use of bevacizumab as an anti-vascular endothelial growth factor- $\alpha$  (VEGF- $\alpha$ ) antibody, which has shown some improvement in progression-free survival in patients with advanced or relapsed disease when used alone or in conjunction with mTOR inhibitors, is the most promising [33]. In clinical trials, EGFR inhibitors, HER2/neu inhibitors, and PI3K-PTEN-AKT-mTOR inhibitors have showed modest effect [32,33]. Metformin has shown encouraging benefits in lowering the rate and risk of cancer death in persons with diabetes [33]. In the endometrial population, these agents' indications are still being investigated. Because this protein is abundantly expressed in EC, current trials are examining the role of immunotherapy, specifically programmed cell death protein-1 (PD-1) inhibitors.<sup>34</sup> In addition, therapeutic trials for this patient population are looking at vaccination, adoptive cellular therapy, bispecific T-cell engager antibodies, cytokines, and immunomodulation [34]. Endometrial cancer that spreads throughout the body is generally considered incurable and has a terrible prognosis. Single drugs have been studied in a number of GOG investigations (etoposide, dactinomycin, oxaliplatin, paclitaxel, pyrazoloacridine, liposomal doxorubicin, flavopiridol, topotecan, irifolven, and bevacizumab) and in recurrent endometrial cancer, alternating courses of megestrol acetate and tamoxifen were used, with response rates ranging from 0% to 31% and 6-month progression free survival rates ranging from 0% to 43% [35]. Although there have been significant improvements in endometrial cancer research in recent years, there is still more work to be done as we enhance our understanding and treatment of the disease. The focus will be on properly categorizing malignancies so that patients can be enrolled in clinical trials that are tailored to their needs [36]. A randomized phase III trial in women with endometrial cancer and high-intermediate risk factors is now recruiting participants to evaluate the usefulness of an integrated clinicopathological and genomic risk profile in guiding adjuvant therapy. paclitaxel, carboplatin, and pembrolizumab in detectable advanced or recurrent endometrial cancer in a phase II trial. In patients with high-risk endometrial cancer, a phase II trial of vaginal cuff brachytherapy followed by adjuvant treatment with carboplatin and dose-dense paclitaxel was



conducted. In cervical, upper vaginal, and uterine malignancies, a phase I study of the Wee I kinase inhibitor AZD1775 in conjunction with radiation and cisplatin was conducted [36]. In women with recurrent, persistent, or metastatic endometrial cancer, a randomised phase II research compared single-agent olaparib, single-agent cediranib, or combination cediranib/Olaparib and numerous trials combining checkpoint inhibitors, immunotherapy, tyrosine kinase inhibitors, PARP inhibitors, and/or anti-angiogenic inhibitors [36].

#### 4. CONCLUSION

Endometrial carcinoma is a fairly common malignant tumor of the female reproductive system that should be screened for DNA mismatch repair gene mutations. Several molecularly targeted treatments, such as mTOR inhibitors and antiangiogenic drugs, have been investigated in endometrial cancer. Patients with unresectable illness may get nonsurgical treatment in the form of primary radiation with or without chemotherapy, or chemotherapy alone with carboplatin and paclitaxel. However, hormonal therapy might potentially be used to treat people who are medically inoperable but dont want surgery, radiation, or cytotoxic chemotherapy. PARP inhibitors, immunotherapies such as anti-PD-1 inhibitors, and methods to improve the efficacy of hormone treatment are presently the focus of future research.

#### CONSENT

As per international standard or university standard, patients written consent has been collected and preserved by the author(s).

#### ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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