Emerging drugs for endometrial cancer

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Introduction: From the dualistic classification that divides endometrial cancer (EC) into two types with distinct underlying molecular profiling, histopathology and clinical behavior, arises a deeper understanding of the carcinogenesis pathways. EC treatment comprises different and multimodal therapeutic approaches, such as chemotherapy, radiation therapy or combinations of novel drugs; however, few of these regimens have truly improved progression-free or survival rates in advanced and metastatic settings.

Areas covered: We reviewed the main molecular pathways involved in EC carcinogenesis through a wide literature search of novel compounds that alone or in combination with traditional drugs have been investigated or are currently under investigation in randomized clinical trials.

Expert opinion: The molecular therapies mainly discussed in this review are potential therapeutic candidates for more effective and specific treatments. In the genomic era, a deeper knowledge about molecular characteristics of cancer provides the hope for the development of better therapeutic approaches. Targeting both genetic and epigenetic alterations, attacking tumor cells using cell-surface markers overexpressed in tumor tissue, reactivating antitumor immune responses and identifying predictive biomarkers represent the emerging strategies and the major challenges.

Keywords: biomarker, endometrial cancer, molecular pathway, target therapy

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1. Background

Endometrial cancer (EC) is the most common gynecologic malignancy in industrialized countries, with an incidence rate of 12.9 per 100,000 women per year, in more developed areas [1]. Approximately 52,630 new cases have been diagnosed in 2014 and the annual monitoring of cancer deaths reported almost 8590 events each year in United States (US) [2]. Only in 2008, in the European countries, 12,903 women died from EC, and corrected age-standardized mortality rates have decreased significantly over the past decades in most member states [3].

A dualistic classification divides EC into two types, with distinct underlying molecular profiling, histopathology and clinical behavior: the less aggressive and most common (around 75%) type I and the highly aggressive type II. Type I EC is estrogen-dependent with well and moderate differentiated endometrioid histology and is usually preceded by endometrial hyperplasia. It typically occurs in obese patients and it is associated with diabetes mellitus or hypertension; frequently it is diagnosed at an early stage, secondary to postmenopausal bleeding, with a favorable prognosis (a 5-year survival rate of 80 – 85%) after surgery [4,5]. By contrast, type II EC includes poorly differentiated endometrioid, clear cell and serous carcinomas; it typically occurs in older and thinner women, and is not hormone dependent. Moreover, type II EC is generally more aggressive and has a worse prognosis with a lower 5-year survival rate (35%) than type I [6-10].

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In 68% of cases, EC is diagnosed at an early or localized stage with a 5-year relative survival of 95.3%, otherwise women with regional and distant metastases have a 5-year relative survival of 67.5 and 16.9%, respectively [11,12].

According to a single institution experience on 1303 cases, EC is considered most commonly not an oncologic treat, but a public health dilemma mostly addressed with interventions aimed at promoting an active lifestyle and healthy diet. In fact, reviewing the prospective assessment of survival, morbidity and cost associated with lymphadenectomy, the low and low intermediate risk groups represent 60% of all women with EC and 70% of women with endometrioid lesions. However, overall survival (OS) was 93% and disease-specific survival 99%, indicating that these patients are far more likely to die of comorbidities than of the tumor itself (only 16% of deaths in low-risk patients are cancer-related). On the contrary, 40% of patients with high-risk and stage IV disease have an appreciable risk of treatment failure and death [13]. In this scenario, to improve patient outcome, a strategy different from the conventional treatments represents a necessary medical need.

2. Existing treatment and medical need

Early-stage EC (International Federation of Gynaecology and Obstetrics stage I or II) can be effectively treated with surgery, with or without adjuvant radiotherapy or chemotherapy, while treatment of recurrent or metastatic disease is limited to cytotoxic chemotherapy and, for patients with estrogen receptor (ER)- or progesterone receptor-positive low-grade disease, hormonal therapy is usually recommended [4,14,15].

The first-line chemotherapy choice treatment for metastatic or recurrent EC is paclitaxel and carboplatin, based on its efficacy and reduced toxicity compared with cisplatin-based regimens [16-19]. Although the role of radiation therapy in reducing local recurrence risk in high-risk EC patients is noteworthy, the promising results of PORTEC-3 trial will represent an important contribution to patient-tailored treatment and they will warrant and establish the role of concurrent chemo-radiation with adjuvant chemotherapy in comparison with patients treated with pelvic radiation alone. As far as recurrent EC, there is still no agreement and there are no definitive drugs of choice in spite of the poor prognosis of this subset of patients. They may receive anthracyclines if not used in the first-line setting, cyclophosphamide, 5-fluorouracil, topotecan or progesterin agents. It is noteworthy that the available therapies do not provide long-term disease control, but a modest activity, without evidence of prolonged survival. Many patients demonstrate intrinsic resistance and significant toxicities to these and other therapies, and the palliation of symptoms is considered the main goal at this point of the tumor’s natural history.

As no treatments have been approved for recurrent disease and therapies have been introduced on the basis of Phase III studies, treatment options are extremely limited and they remain an important unmet medical need.

Recently, on a multivariate analysis, time to relapse appeared to have prognostic significance and to be a predictor of response and survival. Similar to recurrent ovarian cancer, the concept of ‘platinum sensitivity’ could be applicable to recurrent EC [20]. In this scenario, novel therapeutic options are in need and several biologic therapies are currently being investigated. In fact, the successful management of these patients depends on the identification and understanding of molecular mechanisms, as the initiation and progression of cancer, thus supporting the possibility to achieve a more tailored therapy, based on the biological tumor profile.

3. Market review

Since 2002, an increase in type I EC incidence rates in US has been observed, in 50 - 74-year-old women (1992 – 2002: 0.6%; 2003 – 2009: 1.6%). It may be related to the widespread decrease in estrogen plus progestin menopausal hormone therapy use, which has been reported to lower EC risk in overweight and obese women [21]. In 2013, in the US, 49,560 new cases of cancer of uterine corpus (6% of all new cases of cancer) and 8190 deaths (3% of all deaths for cancer) have been estimated [2]. According to a projection of the cost of cancer care in the US, between 2010 and 2020, the national cost of cancer care is substantial and expected to increase, because of population changes alone; thus, an increase of 39%, which corresponds to $173 billion, has been estimated. In this regard the national costs of uterus cancer care for 2010 and 2020, using different assumptions of future cancer incidence, survival and increases in the cost of care, have been estimated to be $2.62 and $3.42 billion, respectively. Only in 2010, the average annualized net cost of care in the last year of life phase of care, for patients dying from uterus cancer, was $70,175; while the average annualized net cost of care for the initial phase of care was $26,775 [22]. This increase in costs over time in the base case scenario reflects the population growth and aging. An Ontario population-based descriptive study concerning the costs of cancer care before and after diagnosis for the 21 most common cancers found out that in 2009 the mean overall cost for EC patients who survived beyond 1 year and for patients who died within 1 year from the diagnosis of cancer was about $18,000 and $38,000 respectively; inpatient hospital admission and chemotherapy combined with radiotherapy contributed to 64 and 9% of the total costs, respectively [23].

The reported estimates and projections may be particularly useful for policy makers, for prioritizing future resources on cancer research, treatment and prevention. Several retrospective studies have evaluated the cost-effectiveness of follow-up in EC patients, showing an urgent need for prospective randomized studies to evaluate the current so-called ‘standard medical practice of follow-up’. According to a French study, approximately two-thirds of the follow-up total cost of EC
was due to systematic examinations (Pap smears and radiography); the annual cost of nonclinical examinations for each patient was €420, and the cost of the clinical examinations for the 351 patients in the study was €90,800 [24]. It is estimated that the cost of follow-up could be reduced considerably, for instance, by tailoring to high- and low-risk groups [24-26].

Otherwise, the expected increase in use of targeted therapies will increase the cost of cancer care. These treatments extend survival in many tumors, for few months at least, target the final stage of cancer and are usually characterized by high costs. In this scenario, questions about costs and benefits or economic health-care analysis are mandatory. Companies are implementing and valuing their drugs, conducting very expensive clinical trials, but it is difficult to sustain the impact that targeted therapies will have in terms of costs with their widespread use. The identification of prognostic biomarkers, which are able to predict response to targeted therapies, might be helpful to individualize treatments and to mitigate costs.

Furthermore, to improve the quality and efficiency of cancer care and make decisions about the resources allocation for cancer prevention, treatment and control, or the individuation of most cost-effective therapeutic strategy, epidemiologic and economic data should be considered.

4. Current research goals

With the purpose of improving the outcome of advanced, metastatic and recurrent disease, it is essential to identify those effective cytotoxic agents in resistant EC to conventional chemotherapies (chemo-refractory tumors), or the supportive agents that alone or in combination with traditional drugs could increase sensitivity to primary chemotherapies. Identification of effective second-line agents for chemo-refractory cancers is one of the principal efforts. Over the past few years several novel cytotoxic agents have been synthesized for the treatment of malignancies, and clinical trials for EC have been conducted using drugs identified as effective for other solid tumors, like ovarian cancer. However, these attempts were ineffective and failed mostly, EC being a heterogeneous and complex disease. Individualized target therapy, based on tumor biological features such as molecular pathways or tumor-specific surface markers, may improve the effectiveness of the second line chemotherapy.

In a recent study, microarray analyses have been used to identify targeted drugs for chemo-refractory cases. The reported results suggest that identification and use of genomic signatures could lead to the identification of new therapeutic candidates that may prove beneficial in this subset of EC [27].

A systematic literature review has been conducted through PubMed-NCBI and the website www.clinicaltrials.gov, to find out the involved molecular pathways in EC carcinogenesis, the new target agents and trials ongoing.

This review will provide the potentially suitable new therapies and strategies for the treatment of EC patients, by focusing on the drugs that are already in clinical development phases.

5. Scientific rationale

EC is a heterogeneous group of tumors with variable pathological, clinical, epidemiological and genetic properties. Although each of these aspects contributes to understand the biology of EC, they must be combined to achieve maximum benefit in patient care. The dualistic model defines EC as ‘endometrioid’ (Type I) and ‘non-endometrioid’ (Type II), and this classification subsequently has shown systematic differences in molecular features [28,29]. Prototypical type I tumors are prone to inactivation of the phosphatase and tensin homolog tumor (PTEN) suppressor gene, which modulates cell division and enables apoptosis [30], and a wide variety of ancillary molecular defects. Thus, the most frequent altered signal pathway is phosphatidylinositol 3-kinase (PI3K)/PTEN/AKT/mTOR [31,32].

Type II EC instead is characterized by inactivation of p53 gene and overexpression of human EGFR 2 (HER-2), a member of the EGFR/ERBB [33].

The upregulation of EGFR [34,35] and VEGF [36], the dysregulated microRNA (miRNA) [37] and the activation of cancer stem cell (CSC)/epithelial-mesenchymal transition (EMT) programs are involved in oncogenesis and progression of both cancer types [38].

While type I tumors have a very specific genetic instability, as the mismatch repair defects, by involving MSH1, hMLH1 genes, or silencing of tumor suppressor genes, including PTEN [39], adenomatous polyposis coli [40], RAS-associated domain family member protein 1 (RASSF1A) [41] and E-cadherin [42], the genetic instability in type II tumors instead is manifested globally at the chromosomal rather than microsatellite level, frequently demonstrating high-order aneuploidy, although there is an intact mismatch repair mechanism [43].

Another important mechanism for epigenetic regulation of gene expression is involved in noncoding RNAs, specifically small regulatory miRNA, able to bind to their mRNA targets. An miRNA may possibly have multiple target genes and concurrently influence different cellular signal pathways [44], participating in a wide variety of biological functions of tumor, like cell proliferation, differentiation, migration, apoptosis, and recently EMT/cancer-stem-cell-like features. The use of antibodies against cell-surface markers overexpressed in EC tissue that might deliver targeted drugs to EC cells more specifically is the strength of miRNA-based therapies, with fewer side effects on normal tissue. The cell-surface markers overexpressed in EC are the tight junction proteins, like claudin-3 and claudin-4, highly expressed in endometrioid, serous papillary, and clear-cell EC, the folate receptor α, a membrane-bound molecule, and the mesothelin, a
glycosylphosphatidylinositol-linked cell-surface antigen; all of them are upregulated more frequently in serous than in endometrioid EC. The trophoblast cell-surface marker (Trop-2) is a cell-surface glycoprotein, which is highly expressed in both types of EC, while epithelial cell adhesion molecule, a reliable marker for tumor-initiating cells, and L1 cell adhesion molecule (L1CAM), a key driver for tumor cell invasion and EMT, are highly expressed among serous EC.

In the PORTEC trials, tumor samples of 865 (75.8%) patients were available for L1CAM expression analysis by immunohistochemistry. Positive L1CAM expression was significantly correlated with risk of distant recurrence, and tumors with the highest expression levels (> 50% positive) had the strongest risk of distant recurrence.

Finally, the EphA2 tyrosine kinases receptor that regulates cell adhesion, proliferation, migration and angiogenesis is overexpressed in a high proportion of type I EC, correlating with advanced disease and poor prognosis.

The Cancer Genome Atlas Research Network proposed an innovative classification of EC, with probable influence on treatment recommendations, based on an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas. A multiplatform analysis that classified EC into four categories, POLE ultramutated, microsatellite instability hypermutated, copy number low and copy number amplified, has been conducted, while serous EC shares genomic features with ovarian serous and basal-like breast cancers.

Another aspect to consider in EC carcinogenesis is the rare population of CSCs, which have the ability to self-renew, initiate tumor growth and give rise to the heterogeneous tumor cell mass. Growing evidences suggest that CSCs support tumor maintenance. Specific inhibitors targeting the CSC/EMT signal pathways in EC would prevent tumor cell increase, invasion and ability to acquire CSC properties, like a rising capacity to metastasize. Other potential therapeutic candidates for EC treatment include static (inhibitor of STAT3-Signal transducer and activator of transcription 3) that can suppress EGF-enhanced invasive behavior of EC cells, rapamycin (mTOR inhibitor) and CD133 antibody-cytotoxic drug.

Therefore, tumor cells induce immunosuppression by the production of immunosuppressive factors, such as TGF-β, IL-10, VEGF and COX-2. Undergoing EMT, cells can acquire both aggressive and immunosuppressive properties, with the activation of Wnt/β-catenin pathway and STAT3-related pathway, seeming attractive targets for EC immunotherapy. Considering the recent important findings in the promotion of EC growth and metastasis, several clinical trials are assessing the efficacy of the new drugs targeting these signal pathways (Figure 1), and in this context, the role of nanotechnology could be crucial to develop a more effective delivery system for targeted agents. A subsequent dilemma is if a target therapy can be selective against CSC, without destroying normal stem cells. Concerning toxicity and the side effects associated with targeted therapies, they include ‘Off-target’ adverse effects caused by a drug binding to an unexpected target, and ‘On-target’ adverse effects as a result of a drug binding to its intended target that is not only present in tumor cells, but also found in normal tissue.

Unfortunately, a part of patients, due to a primary resistance, do not respond to targeted agents, and among those who initially respond, some may acquire a resistance to targeted drugs. The most frequent reported cause of resistance is the genetic heterogeneity, like presence of point mutations, deletions and amplifications of genomic areas. Moreover, also epigenetic changes, or the generation of cancer cells with stem-cell properties, might cause resistance to multiple molecular drugs. Therefore, new therapies, attacking multiple crucial pathways, inhibiting the cross-talk between different signals, may be effective to overcome the resistance to molecular agents in EC.

6. Competitive environment

6.1 Epothilones

The epothilones are a novel class of non-taxane microtubule-stabilizing agents with a mode of action similar to paclitaxel. Ixabepilone (Ixempra, by Bristol-Myers Squibb) is a semisynthetic analog of epothilone B, with low susceptibility to tumor resistance mechanisms. It has shown preclinical activity against paclitaxel-resistant and paclitaxel-insensitive breast, lung and colon cell lines, and in 2007 it has received US FDA approval as a monotherapy option in metastatic breast cancer, resistant or refractory to conventional drugs.

Ixabepilone was chemically modified to improve antitumor activity relative to epothilone B; in vivo it showed antitumor activity, as a single agent or in combination with various anticancer agents, against a broad spectrum of tumor types, including those that overexpress P-glycoprotein and/or are resistant to multiple agents like taxanes, anthracyclines, platinum and vinca alkaloids.

Its activity has been investigated in the GOG-0129P, a single-arm Phase II study, conducted by Dizon et al., in advanced or recurrent EC, previously treated with one prior chemotherapeutic regimen, including either paclitaxel or docetaxel. Fifty patients received ixabepilone 40 mg/m² as a 3-h infusion on day 1 of a 21-day cycle, showing modest activity of limited duration as a second-line treatment, with an overall response rate of 12% and a 6-month PFS of 20%. The toxicity was predominantly myelosuppressive, and grade 3 toxicities were neutropenia (52%), leukopenia (48%), gastrointestinal (24%) and neurologic (18%) [57].

The most recent preliminary results, from a Phase III, randomized IXAMPLE2 study of ixabepilone (40 mg/m²) administered every 21 days versus paclitaxel (175 mg/m²) or doxorubicin (60 mg/m²) administered every 21 days, in advanced previously pretreated EC patients, show an OS of 10.9 months versus 12.3 months (p < 0.0397) and a PFS of 3.4 versus 4.0 months (p < 0.8011), respectively.
6.2 Target therapy

6.2.1 Zoptarelin doxorubicin

Luteinizing hormone-releasing hormone (LHRH), also known as GnRH, is a hormonal decapeptide produced by the hypothalamus, which plays a pivotal role in the regulation of the pituitary-gonadal axis, influencing sex steroids production. Because sex steroids have been implicated in the development of breast and other gynecological cancers, the role of LHRH and its receptor in these tumors has been studied.

While breast cancers were found positive for LHRH receptors in up to 50% of cases, >80% of ovarian and ECs have been reported to have functional binding sites for LHRH [58-60], and treatment of EC cells with LHRH analogs in vitro resulted in growth inhibition [61], although clinical trials have demonstrated insufficient activity of LHRH agonists [62]. Therefore, cytotoxic LHRH analog as zoptarelin doxorubicin (AEZS-108, developed by Aeterna Zentaris) uses LHRH receptors for targeted chemotherapy [63,64]; it is an LHRH-cytotoxic hybrid molecule, composed by doxorubicin chemically linked to the carrier molecule D-Lys-LHRH (an LHRH agonist), which enables the specific binding and selective uptake of the hybrid molecule by tumors expressing receptors for LHRH (‘drug targeting’). After internalization, zoptarelin doxorubicin induces apoptosis in human breast, endometrial and ovarian cancer cells [64]. It might be an ideal compound for targeted therapy for tumor cells positive for LHRH receptors, demonstrating less toxicity and more efficacy than doxorubicin in LHRH receptor-positive human endometrial and ovarian cancers xenotransplanted into nude mice [65].

Recently, zoptarelin doxorubicin has been investigated in women with stage III or IV or recurrent, LHRH receptor-positive EC, showing activity and low toxicity, thus supporting the principle of receptor-mediated targeted chemotherapy. From April 2008 to November 2009, 44 patients were included in the multicenter Phase II trial; prior anthracycline therapy was not allowed. The reported median time to progression was 7 months, and the median OS was 15 months; the most frequently adverse effects were grade 3 or 4 neutropenia (12%) and leucopenia (9%) [66]. A multicenter, Phase III, randomized controlled study comparing zoptarelin doxorubicin (267 mg/m² in 2-h intravenous infusion every 21 days) with doxorubicin (60 mg/m² in 1-h intravenous infusion every 21 days) as second-line therapy for locally
advanced, recurrent or metastatic EC is actually ongoing; the results are widely expected.

6.2.2 Antiangiogenetic agents
Over the past three decades, a wealth of scientific evidence has accumulated, demonstrating the importance of angiogenesis in solid tumor growth and metastasis. Formation of new vasculature is essential for the delivery of both oxygen and the nutrients required for tumor cell proliferation. Tumor angiogenesis is controlled by a number of different pathways. A key mediator of angiogenesis is VEGF-A, which is the prototypic member of a closely related group of growth factors consisting of six secreted glycoproteins: VEGF-B, VEGFC, VEGF-D, VEGF-E and placental growth factor (PLGF). The VEGF group of growth factors has become a focal point for targeted approaches to treating cancer.

The VEGF-A system has been shown to improve PFS and/or OS in a series of large, randomized Phase III clinical trials in a wide range of tumor types. Therefore, great expectations arise from the results of a retrospective study on 11 patients with advanced/recurrent ECs who received bevacizumab combination therapy. All patients had multisite disease and were heavily pretreated with a median of three previous chemotherapy regimens. The median PFS was 5.4 months for the entire cohort and 8.7 months for those who achieved clinical benefit. The reported median PFS and median OS were 2.9 and 14.5 months, respectively. Concerning toxicity, aflibercept appeared to be too toxic; grade 3 - 4 cardiovascular adverse events appeared in 28% of patients, and two treatment-related deaths occurred, due to gastrointestinal perforation and arterial rupture. The rate of treatment discontinuation observed was higher than that (6%) with bevacizumab in a similar clinical setting. Maybe, the use of a different schedule could allow further investigations.

6.2.3 Agents interfering with growth factor receptors: monoclonal antibodies and tyrosin kinase inhibitors
Among the peptide growth factor receptors frequently implicated in EC, there are members of type I receptor tyrosine kinase family, which includes HER1 (EGFR), HER2/neu (erbB2), HER3 and HER4.

In serous EC, the reported rates of HER2 overexpression range between 14 and 80% and it may have a prognostic value and potential role in the therapy of advanced and/or high-grade endometrioid carcinomas.

Aflibercept (Zaltrap by Sanofi) is a novel VEGF ligand-binding fusion protein that serves as a ‘decoy receptor’ for VEGF, and provides strong, picomolar binding affinity for PLGF. Coleman et al. conducted the first investigation of aflibercept in the treatment of recurrent or persistent EC patients. In this Phase II study by GOG, aflibercept was administered every 2 weeks to 44 patients, after prior chemotherapy. Unfortunately, there were not complete responders, only 5 patients (7%) achieved a partial response and 18 patients (41%) were progression free at 6 months. The reported median PFS and median OS were 2.9 and 14.5 months, respectively. Concerning toxicity, aflibercept appeared to be too toxic; grade 3 - 4 cardiovascular adverse events appeared in 28% of patients, and two treatment-related deaths occurred, due to gastrointestinal perforation and arterial rupture. The rate of treatment discontinuation observed was higher than that (6%) with bevacizumab in a similar clinical setting. Maybe, the use of a different schedule could allow further investigations.

Trastuzumab (Herceptin by Hoffmann-La Roche) is an anti-HER2 monoclonal antibody. The GOG undertook a Phase II trial of trastuzumab as single agent, to evaluate its activity against advanced or recurrent HER2-positive EC. Thirty-four women were enrolled, and no major tumor responses, 12 stable diseases and 18 progression diseases were observed. Neither HER2 overexpression nor HER2 amplification appeared to be associated with PFS or OS, demonstrating absence of activity against EC. Serous and clear cell endometrial carcinomas appear to be more likely to demonstrate HER2 amplification.
The combination of trastuzumab with conventional chemotherapy is actually investigated by the Yale University, comparing carboplatin and paclitaxel with or without trastuzumab in serous EC (NCT01367002).

Gefitinib (Iressa by AstraZeneca Pharmaceuticals) is a potent, specific inhibitor of EGFR tyrosine kinase activity, binds to the ATP-binding site on the EGFR kinase domain with a higher affinity than ATP itself and thereby inhibits receptor activation. It has been tested as a therapeutic agent against various malignancies in which the EGF/EGFR pathway is active.

The GOG conducted a Phase II study to evaluate gefitinib activity in persistent or recurrent EC patients. Twenty-six patients received 500 mg oral gefitinib daily until progression or severe toxicity, four patients experienced a PFS >6 months and one had a complete response that was not associated with an EGFR mutation. Therefore, they found that the concentration of soluble EGFR in pretreatment serum was positively correlated with OS, but not with responsiveness to gefitinib in this small patient cohort [73].

Lapatinib (Tyverb by GlaxoSmithKline) is a synthetic small-molecule inhibitor of the HER2 and EGFR tyrosine kinases. The therapeutic potential of lapatinib for the treatment of EC has been explored in a panel of human EC cell lines [74]. A Phase II trial was performed to evaluate the efficacy and safety of lapatinib in persistent/recurrent EC. A new mutation (E690K) of EGFR, in exon 18, which occurred in patient with a partial response and progression-free survival extending past 6 months, has been recently identified, suggesting that even if lapatinib has a limited activity in unselected cases, it may be beneficial in some cases of EC [75].

6.2.3.1 mTOR inhibitors
mTOR inhibitors: Alterations in the PI3K pathway, which regulate cell proliferation and differentiation, are prevalent in EC due to PIK3CA mutation and loss of PTEN. In EC, the most common mechanisms of PI3K pathway activation are loss of PTEN tumor suppressor function and activating mutations in the catalytic PI3K subunit p110 encoded by the PIK3CA gene, which have been identified in 50 – 80% and 25 – 40% of EC, respectively [76]. Preclinical studies have demonstrated that PI3K pathway inhibition can impair the proliferation of endometrial carcinoma cells; collectively these data have provided rationale for Phase I and Phase II clinical trials. The mTOR, an intracellular serine/threonine protein kinase, located at a central point in a variety of cellular signal cascades, is a downstream mediator of the PI3K pathway, and it has been identified as a major link in carcinogenesis. Consequently, inhibitors of mTOR, including temsirolimus (Torisel by Pfizer), an intravenously administered agent or everolimus (Afinitor by Novartis), an oral agent; and ridaforolimus (by Ariad), have been developed and assessed for their safety and efficacy in patients with EC, either alone or in combination with other anticancer agents.

The NCIC Clinical Trials Group conducted a Phase II trial, which evaluated single-agent activity of temsirolimus, 25 mg intravenously weekly in q28 cycles, in women with recurrent or metastatic chemotherapy-naïve or chemotheraphy-treated EC. It showed encouraging results, independent of PTEN status, but higher in chemotherapy-naïve patients (14% had partial response and 69% had stable disease as best response) than in chemotherapy-treated patients (4% had partial response and 48% had stable disease) [77].

Goodwin et al. explored the relationship between early treatment-related toxicity and efficacy outcomes to temsirolimus. They found that women previously treated with chemotherapy were at 7.37 times greater risk of progression and experienced 20.9% increased tumor growth compared to chemotherapy-naïve women, but molecular markers were not predictors of response or progression [78]. Also, everolimus demonstrated efficacy and acceptable tolerability in patients with chemotherapy-refractory advanced or metastatic EC. The ENDORAD Phase II study showed a median PFS and OS of 2.8 and 8.1 months, respectively, and the most common adverse events were anemia (100%), fatigue (93%), hyper-cholesterolaemia (81%) and lymphopenia (81%) [79].

6.3 DNA-interacting agents
Traibectedin (Yondelis, by PharmaMar) is an anticancer marine-derived drug that had gained much attention because of its unique mechanism of action and the demonstration of...
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<td>Launched</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Bristol-Myers Squibb</td>
<td>Derivative of epothilone B</td>
<td>Breast cancer</td>
<td>Launched</td>
<td>Protein kinase inhibitor</td>
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<td>Lapatinib</td>
<td>GlaxoSmith Kline</td>
<td>ErbB-2 and EGFR dual kinase inhibitor</td>
<td>Breast cancer</td>
<td>Launched</td>
<td>ErbB-2 tyrosine kinase inhibitor</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>EGF antagonist</td>
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<td></td>
<td>Tyrosine kinase inhibitor</td>
</tr>
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<td></td>
<td></td>
<td>ErbB-1 tyrosine kinase inhibitor</td>
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<tr>
<td>Ridaforolimus</td>
<td>Ariad</td>
<td>mTOR inhibitor</td>
<td>Osteo sarcoma, soft tissue sarcoma</td>
<td>Pre-registration</td>
<td>VEGF receptor antagonist</td>
</tr>
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<td>Temsirolimus</td>
<td>Pfizer</td>
<td>Sirolimus analog cell-cycle inhibitor</td>
<td>Renal cancer, non-Hodgkin’s, lymphoma</td>
<td>Launched</td>
<td>Angiogenesis inhibitor</td>
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<tr>
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<td>Cell-cycle inhibitor</td>
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<td>Immunosuppressant</td>
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<td>Protein kinase inhibitor</td>
</tr>
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<td>Trastuzumab</td>
<td>Hoffmann-La Roche</td>
<td>anti-HER-2 MAb</td>
<td>Breast, gastrointestinal, esophageal</td>
<td>Launched</td>
<td>EGFR 2 antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cancers</td>
<td></td>
<td></td>
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<tr>
<td>Zoptarelin</td>
<td>AEterna Zentaris</td>
<td>Conjugate of a doxorubicin analog and a peptide carrier targeting</td>
<td>Phase III</td>
<td></td>
<td>DNA topoisomerase II inhibitor</td>
</tr>
</tbody>
</table>

FGFR: Fibroblast growth factor receptor; HER-2: Human epidermal growth factor receptor 2; PI3K: Phosphoinositide 3-kinase.
Emerging drugs for endometrial cancer

clinal activity in ovarian cancer as well as other solid malignancies.

This novel drug has been investigated in EC also, unfortunately showing minimal antitumor activity in pretreated population of women with persistent or recurrent disease, with a median time to progression and PFS both of 1.8 months (95% CI: 1.4, 2.9), and median OS of 6.7 months (95% CI: 5.2, 13.9) [84].

A Phase II Study (NCT00050440) of trabectedin in patients affected by persistent or recurrent EC is currently ongoing.

7. Potential development issues

Recently, increasing knowledge about the molecular biology of cancer and better understanding of the genetic basis of EC have led to the investigation of new targeted therapies that inhibit the cellular signal pathways involved in cell growth and proliferation (e.g., mTOR inhibitors, EGFR inhibitors, VEGF inhibitors).

At first, preclinical evidence suggests that fibroblastic growth factor (FGF) pathway should play a major role; in fact, different FGF receptor 2 (FGFR2)-activating mutations, identified in 10% of the primary uterine tumors studied, have oncogenic potential and are required for cell survival in endometrial cell lines expressing mutant FGFR2 [85], highly sensitive to FGFR tyrosine kinase inhibitors. TKI258 developed by Novartis seems a promising multtarget-based drug. It is a potent inhibitor of receptor tyrosine kinase, acting in a direct antitumor activity, mediated by FGFR, platelet growth factor receptor (PDGFR) and c-Kit, and angiogenesis, mediated by VEGFR, FGFR and PDGFR. The activity of TKI258 is currently investigated in a Phase II, open-label, single-arm, nonrandomized, multicenter study evaluating its efficacy as second-line therapy in patients with either FGFR2 mutated or wild-type, advanced and/or metastatic EC. The effects of both TKI258 and the more selective FGFR inhibitor NVP-BGJ398 have been investigated using a panel of 20 molecularly characterized human EC cell lines. Both agents inhibited FGFR2 signaling, induced cell-cycle arrest and significantly increased apoptosis in FGFR2-mutant lines, but the activity of TKI258 was less restricted to FGFR2-mutant lines when compared with NVP-BGJ398. In vivo, they significantly inhibited the growth of FGFR2-mutated EC xenograft models; in addition, TKI258 showed significant antitumor activity in FGFR2 wild-type EC xenograft models including complete tumor regressions in a long-term in vivo study. They both warrant further clinical evaluation in patients with FGFR2-mutated EC, and beyond these cases due to TKI258 greater flexibility in patient selection [86].

An active area of the scientific research is the biomarker assessments and biomarker sample collection from tumor biopsies or blood with the aim of measuring investigational drug pharmacodynamic effects and finding out potentially useful markers for responder identification. The TKI258 protocol provides biomarker assessment (pFGFR, pFRS2 immunohistochemistry, VEGF, bFGF, PLGF, sVEGFR1, sVEGFR2, FGFR and FGF ligand expression, mutation and amplification).

The combination of target therapies is also generating significant interest. There is evidence that both angiogenic and PI3K/AKT/mTOR pathways appeared to be important therapeutic targets in EC; thus, association of bevacizumab and temsirolimus has been studied by the GOG in a Phase II trial for recurrent or persistent EC. Forty-nine patients were eligible and evaluable of the 53 enrolled patients. Both objective tumor response and PFS at 6 months have been achieved; however, this regimen was associated with significant toxicity (two gastrointestinal-vaginal fistulas, one grade 3 epistaxis, two intestinal perforations and one grade 4 thrombosis/embolism) [87]. Furthermore, the combination of ixabepilone plus lapatinib is currently investigated in a Phase I study as second-line treatment in recurrent or persistent EC patients, which overexpresses HER2. Another example of combinatory therapy is the union of TKI258 with fulvestrant. It was discovered that TKI258 enhances ER-α expression in FGFR2-mutant EC cells. Blocking one signal pathway is often not sufficient to cause tumor regression completely; thus, the combination of TKI258, which targets FGFR2, with a selective ER antagonist, fulvestrant, has resulted in a significantly higher inhibition of cell growth than TKI258 treatment alone [88]. Future studies with the combination of target therapies will be guided by strategies to decrease toxicity and increase response rates. Finally, another aspect to consider is the use of novel drugs, which are obtaining encouraging results in other gynecologic malignancies and which may represent a promising strategy. For example, the poly-ADP-ribose polymerase inhibitors have shown promising activity in patients with BRCA1/2 mutation-associated ovarian and breast cancers, and they look hopeful in prostate and pancreatic cancers [89]. A Phase II study (PANDA) is currently ongoing to evaluate whether the PARPi BMN-673, which has shown to be potentially effective in treating cancers known to behave similar to EC, has therapeutic benefit in the treatment of inoperable advanced EC.

Moreover, given the robust activation of the MAP-kinase pathway, which leads to proliferation and survival of low-grade serous ovarian cancer cells, molecular targeting of this pathway (i.e., drugs inhibiting MEK pathway) provides a logical treatment option. Otherwise, a Phase II study is evaluating the activity of the MEK inhibitor trametinib, alone and in combination with GSK2141795, an Akt inhibitor, in women with recurrent or persistent EC.

8. Conclusion

In summary, the duration of advanced EC responses to treatment is short, with PFS of 6 – 9 months and OS of 12 – 15 months with first-line chemotherapy, and shorter
PFS (2 – 3 months) and OS (6 – 8 months) with second-line regimens. Therefore, therapeutic strategy of advanced and/or metastatic EC is a clear unmet medical need and the investigation of new and effective treatments is warranted. Despite the use of combination chemotherapy or the introduction of novel targeted agents alone or in combination regimens, EC prognosis remains poor.

In fact, a consistent low response rate (rarely exceeding 10%) and short PFS (generally < 3 months) have been seen in almost all studies, including the recent trials exploring the activity of novel, selective agents targeting specific molecular pathways and mediators of signal transduction for cell proliferation, survival and angiogenesis (e.g., tyrosine kinase inhibitors, antiangiogenics and mTOR inhibitors).

The combination of systemic therapy with radiation therapy may represent an important modality of treatment for EC patients. PORTEC-3 is a Phase III trial looking at radiotherapy and chemotherapy after surgery with the aim of finding out if it is better to have radiotherapy and chemotherapy after surgery for womb cancer than radiotherapy on its own, and learning more about the side effects of these treatments and how they affect quality of life (ClinicalTrials.gov NCT00411138).

Otherwise, the GOG 258, a randomized Phase III trial, compares cisplatin and tumor volume-directed irradiation followed by carboplatin and paclitaxel with carboplatin and paclitaxel for optimally debulked, advanced EC. Improvement of recurrence-free survival and OS are the main objectives of this study (ClinicalTrials.gov NCT00942357).

Several studies have demonstrated that the treatment-free interval is the most important factor in predicting the effectiveness of chemotherapy in recurrent EC; applying the concept of ‘platinum sensitivity’ to recurrent EC, platinum-free interval may be considered a predictor of response to second-line platinum-based chemotherapy and also of survival in patients, who received a platinum agent during first-line chemotherapy.

More results are awaited from several ongoing randomized clinical trials that compare conventional treatments with target-based therapies alone or combined with cytotoxic drugs.

9. Expert opinion

EC is a heterogeneous disease requiring different treatment approaches, and although there is a wide range of strategies under investigation, chemotherapy or radiation therapy or combinations to novel drugs, few of these regimens have truly improved progression or survival rates. Therefore, the lack of a real improvement in outcome over decades of clinical trials highlights the desperate need for innovative approaches to treatment.

A further investigation into the use of the novel agents in combination with standard chemotherapeutic regimens may prove to be the most useful approach but a deeper understanding of the molecular carcinogenesis pathways, from angiogenesis to mTOR inhibition, is likely key to the evolution of new, more active, agents.

In this regard, the Gynaecologic Oncology Group is currently conducting a randomized Phase II trial (GOG-086P) of carboplatin-paclitaxel combined with bevacizumab or temsirolimus or ixabepilone, as initial therapy for measurable stage III, stage IV or recurrent EC.

Actually, ixabepilone reported the most promising results, a 12% ORR as second-line therapy, associated with a 60% rate of disease stabilization and a 20% PFS rate at 6 months [56], but also, bevacizumab reported interesting results as a single agent in this patient population [67] (RR of 15.1%, 6-month PFS rate of 35.8%, median PFS of 4.2 months, median OS of 10.5 months).

The use of doxorubicin as second-line chemotherapy, in spite of its reported moderate activity, whether as non-liposomal or pegylated liposomal doxorubicin formulation, is under investigation in the Phase III AEZS-108-050 trial, in which doxorubicin is the comparator drug.

The molecular therapies tested in clinical trials and mainly discussed in this review are potential therapeutic candidates for more effective and specific treatments against EC progression and metastasis. There are still challenges that might remain regarding drug resistance and unexpected side effects on normal tissues, by using biologic drugs, and future study will be guided by strategies aimed to decrease toxicity and increase response rates. For the cohort of patients with urgent need of novel therapies, the enrollment into the Phase I trials at diagnosis of EC may represent a valid option.

But, in the era of genomics, despite the tumor complexity, an increased knowledge about molecular characteristics of cancer provides the hope for the development of better therapeutic approaches. A deeper understanding of EC carcinogenesis may determine implications for treatment and for basic, translational and clinical research.

New studies that aim to target both genetic and epigenetic alterations (noncoding miRNA) and to specifically attack tumor cells using cell-surface markers overexpressed in tumor tissue are emerging. New strategies to disrupt the CSC/EMT-dependent signals and reactivate antitumor immune responses would represent a new hope for the massive destruction compartments in EC. But, the major effort remains the identification of the best treatment on the basis of tumor phenotype and genotype, together with the identification of predictive biomarkers to select those patients who may benefit from these drugs mostly.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
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Emerging drugs for endometrial cancer

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