Targeting the mTOR/4E-BP Pathway in Endometrial Cancer

Sharmilee Bansal Korets¹, Sarah Czok¹, Stephanie V. Blank¹,³, John P. Curtin¹,³, and Robert J. Schneider²,³

Abstract

Endometrial cancer is the most common gynecologic malignancy. Although it is highly treatable in the early stages of disease, therapies for advanced and recurrent disease are rarely curative. A molecular and genetic understanding of endometrial cancer involves the mTOR signaling pathway, an emerging target for treatment of type I disease (the most common presentation). Endometrial cancers show a significant reliance on the mTOR pathway for survival, and studies to date have revealed a clinical advantage in targeting this pathway. Less well developed in the study of endometrial cancer is an understanding of mTOR signaling to its major downstream effector, translational control. Given the poor rate of success for treatment of late-stage endometrial cancer, increasing attention is being directed to the development of new therapeutic approaches, including targeting the mTOR pathway. Here, we discuss the potential benefit of targeting mTOR combined with existing chemotherapies by monitoring its impact on translational regulatory pathways and key translation targets in endometrial cancer. We also highlight laboratory and clinical research findings that will provide new avenues for future research and clinical development. Clin Cancer Res; 17(24); 1–11. ©2011 AACR.

Introduction

Endometrial cancer is the most common gynecologic malignancy and the fourth most common malignancy in American women, with 43,470 new diagnoses and 7,950 deaths for the year 2010 (1). Although the majority of endometrial cancers are diagnosed at an early stage of disease, conferring a favorable prognosis, women who are diagnosed with advanced or recurrent disease have far worse survival rates and limited adjuvant treatment options. In the United States, ~15% of endometrial cancers are diagnosed at stage III or IV, with a 5-year survival rate of 20% to 50% depending on grade and histologic subtype (2). Over the past 30 years, little significant improvement has been seen in the survival of patients with advanced disease (3).

Endometrial cancers are commonly classified into 2 histologic subtypes (4): endometrioid (type I) and nonendometrioid (type II). Each has distinct risk factors, clinical behaviors, and natural histories. Type I tumors are the most common (85%), primarily early stage at diagnosis in postmenopausal, obese women over the age of 50, and estrogen-dependent in a background of atypical hyperplasia. Type II lesions (15%) are primarily comprised of serous and clear-cell histologies. Type II tumors are more aggressive and associated with extraterine spread, later-stage disease, and poorer prognosis.

Type I and type II malignancies also have distinct molecular and genetic characteristics (5). Type I endometrial cancers exhibit a high frequency of microsatellite instability and loss-of-function mutations in the phosphatase and tensin homolog PTEN tumor-suppressor gene. Type II cancers more frequently show p53 mutations.

Patients with advanced disease typically receive adjuvant chemotherapy [cisplatin–doxorubicin–paclitaxel (6)] with or without radiation after surgical staging. As a result of poor toxicity profiles, the molecular targets and signal transduction pathways involved in endometrial cancer are now under investigation in multiple phase I and II trials (7).

Here, we focus on the role of mTOR inhibition in future treatment strategies and downstream effects on protein synthesis, with the goal of increasing new combination therapeutic approaches and the use of novel biomarkers to achieve better treatment response. Indirect (allosteric) mTOR inhibitors, known collectively as rapalogs, show activity in the treatment of type I disease. Therefore, rapalogs represent attractive investigational drugs for the management of endometrial cancer due to their relationship with the PTEN signaling pathway, which is frequently mutated in type I endometrial cancers. However, a new class of catalytic mTOR inhibitors that act directly on mTOR have been introduced in phase I dose-escalation trials. These drugs more effectively inhibit mTOR in both of its signaling complexes, mTORC1 and mTORC2. Taking into account the emergence of direct mTOR inhibitors and the developing knowledge about the effects of mTOR inhibition on protein synthesis, we review the present understanding of the role of the mTOR–translational control
Translational Relevance

Endometrial cancer remains the most common gynecologic malignancy. Although it is highly curable by surgery when diagnosed at an early stage and grade, the burden of advanced stage and recurrent disease is substantial. Current combination therapies are highly toxic and of limited efficacy for the treatment of patients who require systemic therapy. Advances in the molecular genotyping of endometrial cancers have led to an intense focus on molecularly targeted agents that act on the mTOR pathway, and this approach has shown some of the best responses in the treatment of advanced and recurrent disease. In this short review, we explore the relationship between endometrial cancer and the mTOR pathway and its downstream regulation of protein synthesis. We suggest that there is a critical need to match experimental mTOR therapeutics with existing chemotherapies by optimizing the impact on translational regulatory pathways in the treatment of endometrial cancer.

Major Molecular Alterations in Type I Endometrial Cancer: A Brief Overview

The genes that are commonly mutated in type I endometrial cancers are largely responsible for the regulation of signal transduction, which is involved in normal cell replication and cell–cell adhesion. Thus, disruption of these pathways and functions leads to abnormalities in cell proliferation and to the ability to invade or metastasize. The most frequent alterations in type I endometrial cancers are summarized in Table 1. Because this area has been extensively reviewed in the past (8, 9), we provide only a summary of key features that also affect mTOR and translational regulation in this disease.

**Table 1. Molecular alterations in type I endometrial cancer**

<table>
<thead>
<tr>
<th>Molecular alteration</th>
<th>Frequency</th>
<th>Reference</th>
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<tbody>
<tr>
<td>PTEN</td>
<td>50–83%</td>
<td>Hecht and Mutter (8)</td>
</tr>
<tr>
<td>PI3KCA</td>
<td>36%</td>
<td>Liu et al. (80)</td>
</tr>
<tr>
<td>β-catenin</td>
<td>20–40%</td>
<td>Bansal et al. (9)</td>
</tr>
<tr>
<td>K-ras</td>
<td>10–30%</td>
<td>Hecht and Mutter (8)</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>20%</td>
<td>Basil et al. (81)</td>
</tr>
<tr>
<td>LKB1</td>
<td>20%</td>
<td>Lu et al. (25)</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>10–20%</td>
<td>Bansal et al. (9)</td>
</tr>
<tr>
<td>p53</td>
<td>10–20%</td>
<td>Bansal et al. (9)</td>
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**PTEN**

The most common genetic mutation in type I endometrial cancers (83%) occur in the phosphatase gene PTEN, with loss or mutation (8, 9). PTEN is a tumor-suppressor gene, the loss of which plays a major role in stimulating the phosphoinositide 3-kinase (PI3K)–AKT–mTOR pathway (10). PI3K–AKT–mTOR upregulation modestly upregulates protein synthesis and more strongly upregulates translation of survival, angiogenesis, and so-called oncogenic mRNAs (ref. 11; Fig. 1).

PTEN has lipid and protein phosphatase activity (10, 12, 13). The lipid phosphatase domain maintains cell-cycle arrest at the G1–S checkpoint, upregulates AKT-dependent proapoptotic pathways, and downregulates Bcl-2–dependent antiapoptotic pathways (14). PTEN controls the levels of phosphorylated AKT by opposing PIK3CA activity. The protein phosphatase domain inhibits focal adhesion formation, cell spreading, and migration (15). Increased mTOR activation and protein synthesis are necessary to sustain these activities (11). Studies of PTEN knockout mice have helped elucidate its role in endometrial cancer. In one study (16), 100% of the mice examined developed hyperplastic lesions in the endometrium and 20% developed endometrial carcinoma as a result of heterozygous mutations in PTEN.

**PIK3CA**

The PIK3CA gene encodes the α catalytic subunit of PI3K. This lipid kinase catalyzes production of PIP3, resulting in the activation of multiple downstream targets, most notably AKT, leading to mTOR activation, and thus promoting cell proliferation and survival (17). As noted above, this pathway is upregulated in a majority of endometrial cancers. Thirty-six percent of patients with endometrial cancer have PIK3CA mutations, and 26% have concurrent PTEN and PIK3CA mutations (18). PIK3CA mutations are strongly associated with endometrioid histology and a higher stage, and show a trend toward increased incidence of lymphovascular invasion (19).

**KRAS**

The KRAS gene is a proto-oncogene encoding a small inner plasma membrane GTPase that is involved in cell signaling related to growth and differentiation. KRAS mutations resulting in constitutive activity are present in 10% to 30% of type I endometrial cancers and 16% of hyperplastic lesions. Similar to the PTEN mutation, the frequency of the KRAS mutation is increased in endometrial cancers that show genomic instability (8, 9, 20). Additionally, KRAS mutations stimulate downstream mTOR kinase activity, leading to increased selective translation of mRNAs involved in tumor cell survival, angiogenesis, and proliferation (11).

**Mutation of the LKB1 gene**

LKB1 (also known as STK11) is a serine–threonine kinase that phosphorylates and activates AMPK-dependent
kinase [AMPK (21)]. AMPK senses ATP–AMP levels, thereby regulating cellular metabolism (22). mTOR is inhibited by active AMPK through phosphorylation and activation of the tuberous-sclerosis complex-2 (TSC2) protein, an upstream inhibitor of mTORC1 (ref. 23; Fig. 1). Thus, mutation of LKB1, similar to mutation of PTEN or KRAS, and elevated levels of insulin-like growth factor I (IGF-I) results in strong mTOR activation and upregulation of protein synthesis. Animal models of LKB1 deficiency show a high level of aggressive features in endometrial cancers, ...
consistent with elevated mTOR activity (24). Studies of human endometrial tumors have shown that ~20% are LKB1-negative, and as many as 65% have a functional deficit in the protein (25).

Elevated IGF-I levels

Endometrial cancers are associated with elevated IGF-I expression and activation of the IGF-I signal transduction pathway (26). Whereas estrogen increases IGF-I gene transcription (26), PTEN downregulates IGF-I receptor levels (27), which are typically increased in endometrial cancers (28). The IGF-I pathway thus links loss of PTEN, increased AKT–mTOR activation (29), and estrogen signaling in endometrial cancer. Recently, a direct link was established for the regulation of IGF-I and insulin by the PTEN–AKT–mTOR axis through mTOR target protein Grb10, which when phosphorylated is a negative regulator of insulin signaling and IGF-I (30, 31).

The Role of Hormones in Endometrial Carcinogenesis

Hormones act on the endometrium to modify the genetically predetermined risk of cancer. Estrogen and progesterone have divergent and often opposing effects on the endometrium (8). Estrogen can promote cell proliferation and inhibit apoptosis, whereas progesterone can inhibit proliferation and promote apoptosis and involution (32). Increased proliferative activity can increase the rate of random mutation, possibly accounting for some of the potential carcinogenic effects of estrogen on the endometrium. Further, by promoting cell proliferation, estrogen creates a selective advantage for PTEN mutant clones that have escaped the usual proapoptotic, antiproliferative checkpoints (32). In addition to opposing endometrial cell proliferation, progesterone further counteracts the effect of estrogen by downregulating expression of the estrogen receptor itself. Progestins therefore reduce the proliferative advantage of PTEN mutant cells, leading these clones to involute (8).

The mTOR/4E-BP Translational Control Pathway

Growth factor stimulation and hormone receptor activation, as well as cellular responses to nutrient status, hypoxia, and other physiologic and metabolic alterations, ultimately signal to the protein kinase mTOR (Fig. 1; ref. 33). mTOR is a member of the PI3K–AKT family, which promotes cell proliferation, survival, and angiogenesis (34). mTOR is a serine–threonine kinase that acts on factors in the protein synthesis machinery, integrating signals from a variety of growth factors and nutrients to regulate key metabolic and macromolecular processes, including mRNA translation, cell motility, and ribosome biogenesis. mTOR forms 2 different protein complexes, mTORC1 and mTORC2, that mediate very different functions, in part through mRNA translational control.

mTORC1 is a protein complex that contains mTOR, regulatory-associated protein of mTOR (Raptor), G-protein β-subunit-like protein/LST8 [GβL (33)], and proline-rich AKT substrate 40 kDa (PRAS40). Raptor recruits substrates to mTORC1 for phosphorylation, including the elf4E binding/inhibiting protein (4E-BP, inhibited by mTORC1 phosphorylation) and ribosomal protein S6 kinases-1,2 (S6K-1,2). S6K-1,2 phosphorylates ribosomal protein S6, initiation factor elf4B (stimulating its RNA binding activity and translation), tumor suppressor protein PDCD4 (increasing initiation factor elf4A activity), and translation elongation factor elf2 kinase, thereby inactivating the kinase, and in turn promoting elf2 activity and elongation (Fig. 1).

The second mTOR complex, mTORC2, contains GβL, the protein rapamycin-insensitive companion of mTOR (Rictor), and mammalian stress-activated protein kinase (SAPK)–interacting protein [mSIN1 (35)]. Activation of mTORC2 regulates cytoskeleton organization in response to growth factors and leads to increased phosphorylation (activation) of AKT, which in turn is an upstream activator of mTORC1 and protein synthesis (36). mTORC2 is generally insensitive to inhibition by allosteric mTOR rapalog inhibitors such as sirolimus, but not to small-molecule catalytic mTOR inhibitors. Of importance, rapalog treatment can actually stimulate AKT–mTOR through mTORC2 activation (37–40), which has fueled interest in the clinical development of small-molecule, catalytic-site mTORC1/2 inhibitors.

Rapalog inhibition of mTOR

Amplification of PI3K–AKT, increased transcription, or loss of regulatory control by mutation or deletion of regulators such as PTEN can result in mTOR activation. Loss of PTEN is the primary means for maintenance of increased mTOR activity in endometrial cancer (41), as supported by animal studies (42). Analyses of human type I and type II endometrial cancers have shown a compelling association among PTEN loss, increased mTOR activity, hyperphosphorylation (inactivation) of the translation inhibitor 4E-BP1, increased cancer progression, and reduced survival in type I disease (43). That said, overexpression of mTOR itself in endometrial cancer as a means for increased mTOR activity is actually quite rare (~7% incidence) and may not correlate with disease progression, survival, or even sensitivity to mTOR inhibition (44). In principle, however, the overactive PI3K–AKT–mTOR pathway in endometrial cancer should provide an excellent target for treatment due to an increased requirement for mTOR activity and increased sensitivity when inhibited.

Rapamycin was initially used as an antifungal agent and subsequently was applied as an immunosuppressant for tissue transplant patients. First-generation mTOR inhibitors (also known as rapalogs) include sirolimus (rapamycin), temsirolimus, everolimus, and ridaforolimus. All of these inhibitors are sirolimus analogues that were developed for oral or i.v. administration by derivatization of the C40 hydroxyl group. They inhibit mTORC1 by acting on FK506.
binding protein 12 (FKBP12), an intracellular receptor that activates mTORC1 through a mechanism that remains poorly understood (35). Rapalogs insufficiently inhibit mTOR, with loss of S6K-negative regulation of IRS-1, poor activation of the 4E-BPs, and little inhibition of protein synthesis. Rapalogs used as single-agent inhibitors have also been linked to increased AKT activity due to positive feedback regulation of AKT by mTORC2 (37, 39, 40).

**mTOR-mediated translational control and its implications in endometrial cancer**

The initiation of mRNA translation is generally the rate-limiting step of protein synthesis. A number of features contribute to widely different rates of initiation on different mRNAs, creating a scenario of scalable and remarkably selective translation of different mRNAs in response to physiologic signals (11). Cellular mRNAs contain a 5′ inverted 7-methylguanosine cap that serves as the recognition site for the translation initiation machinery. The cap is recognized by initiation factor elf4E, which in turn recruits the scaffolding protein elf4G and the ATP-dependent RNA helicase, elf4A, that collectively comprise the factor elf4F (45). elf4F interacts with the multisubunit factor elf3, which in turn recruits the 40S small ribosome subunit and the complex containing the initiating methionyl-tRNA, elf2, and GTP (Fig. 1).

mTOR plays a pivotal role in regulating translation initiation through control of elf4F. The majority of mRNAs require cap recognition by elf4E and assembly of the cap-initiation complex to recruit ribosomes and initiate translation. mTOR phosphorylation of the 4E-BPs (4E-BP1 is the major epithelial cell form) promotes cap-dependent mRNA translation by inactivating their elf4F-sequestering activity (46). mTOR also phosphorylates the major form of elf4G (elf4GI). The function of elf4G phosphorylation is unclear, but it may stimulate a structural alteration that promotes greater translation of a subset of mRNAs (47). mTOR phosphorylation activates S6K-1 and S6K-2, which promotes cancer progression (11). In particular, S6K1 phosphorylation of elf4B stimulates elf4A activity and translation (48).

Although increased mTOR activity (34) and levels of protein synthesis are a hallmark of many human cancers, as are increased levels of elf4E, elf4GI, and several other translation factors (11), the selectively increased translation of a specific group of mRNAs that encode proteins involved in angiogenesis, survival, and oncogenic functions is thought to provide the rationale for targeting the increased mTOR activity found in endometrial and other cancers.

**Increased mTOR activation favors selective mRNA translation**

Studies have shown that increased mTOR activity and the increased expression of elf4E and elf4GI primarily favor strong, selectively increased translation of a subset of mRNAs with extensively structured 5′ untranslated regions (5′ UTR) and/or low abundance or multiple upstream open reading frames (49, 50). In general, when mRNAs with these characteristics are increased in translation, they become key players in cancer development, angiogenesis, survival, hypoxia responses, and disease progression (11). Examples include mRNAs that encode proteins for survival (MCl1, survivin, XIAP, and Bcl2), cell-cycle progression (c-myc, ODC1, and cyclin D1), angiogenesis (VEGF-A and FGF2), and response to hypoxia (HIF1α), among others (11).

Increased expression of elf4E/elf4GI and/or increased availability of elf4E or elf4A (through reduced antagonistic PDCD4 levels) are thought to promote greater unwinding by elf4A of 5′ UTR structures and, therefore, to disproportionately promote greater translation of these mRNAs. This in turn is associated with increased malignancy and decreased survival in a variety of human cancers, including endometrioid endometrial cancers (43). Increased expression of elf4E and/or elf4GI or hyperphosphorylation of 4E-BP1 by activated mTOR is similarly associated with higher tumor grade and stage, cancer progression, and reduced survival in a number of human cancers (43). In a recent study, elevated expression of elf4E was observed in more than half of the type I endometrial cancers examined, with the greatest expression found at stages III/IV (51), suggesting that these tumors have a greater sensitivity to mTOR inhibition. The underlying mechanism is thought to be strongly increased translation of select mRNAs. In this regard, understanding the dependence of selectively increased mRNA translation on increased mTOR/elf4E activity in endometrial cancer provides a new paradigm for the design of therapeutic clinical trials. As described below, single-agent and MTD strategies for mTOR inhibitors fail to take advantage of a low-toxicity therapeutic window in which we might be able to achieve selective translation inhibition of oncogenic mRNAs while largely sparing overall protein synthesis.

**Preclinical studies of mTOR inhibition in endometrial cancers**

Rapalog studies in endometrial cancer have focused primarily on expression of mTOR pathway proteins (44, 52–58) and cellular responses to mTOR inhibitors (25, 52, 59–62). Several groups have also investigated the role of small-molecule mTOR kinase inhibitors in endometrial cancer cell lines (59, 63) and the effects of mTOR inhibitors on mouse models of endometrial cancer (3, 64–66).

In multiple studies, investigators have tested the correlation between the mTOR pathway and the control of protein synthesis and the clinical behavior of endometrioid tumors. Activation of mTOR and phosphorylation of 4E-BP1 occur more frequently in advanced-stage and high-grade endometrial tumors, respectively (52), associated with cancer progression and reduced survival (43). Similarly, a trend toward increased activation of the AKT–mTOR pathway was found in patients with progesterone-refractory endometrial hyperplasia (55). Increased signaling in breast cancers through hormone receptors has been linked to increased...
activation of mTOR and, by extension, protein synthesis (67). Surprisingly, however, 2 studies in endometrial cancer revealed no statistically significant correlation between expression or activity of the AKT–mTOR pathway and survival or clinical-pathologic characteristics, including stage, grade, and lymph node involvement (44, 56).

In tissue-culture studies, researchers have further investigated the impact of mTOR inhibition by rapalog treatment on biologic activities and tumor development using endometrial cancer cell lines. Overall, the results indicate that rapalogs are more effective as cytostatic agents than as cytotoxic ones and that they have the ability to potentiate the effects of other cytotoxic chemotherapeutic drugs, including cisplatin and paclitaxel (58–60). In addition, cell culture studies have shown dose-dependent anti proliferative properties of rapalogs as single agents (52, 58, 59, 61, 62). Mirroring human studies, tissue culture studies have shown contradictory results with regard to the impact of PTEN status on rapamycin sensitivity (32, 40, 41, 43). Investigators have also examined rapalog treatment in mouse models of endometrial hyperplasia, and they found that treatment with rapalogs reduced tumor burden, slowed progression of disease, and decreased the incidence of hyperplastic lesions in mice predisposed to hyperplasia (3, 64–66).

**Current clinical trials of mTOR inhibitors in endometrial cancer**

In a number of completed and ongoing phase I and II trials, researchers have investigated the role of oral and parenteral rapalog mTOR inhibitors in advanced and recurrent endometrial cancers (7, 68). All rapalogs, whether administered by oral or i.v. routes, provide similar low biologic exposure and have been shown to inhibit the phosphorylation of 4E-BP1 or S6K1 as surrogate markers of activity in tumor specimens or circulating peripheral blood mononuclear cells (69). Plasma concentrations show a prolonged half-life for sirolimus (~50 hours) compared with temsirolimus (~15 hours), which is converted to sirolimus (70). Using preclinical studies and demonstrated activity in other malignancies as a reference, investigators are developing new regimens with the goal of achieving more tolerable, efficacious treatments for advanced or recurrent endometrial cancer.

Studies have shown a variable response to mTOR inhibition in the treatment of advanced and recurrent endometrial cancer. Treatment-naive endometrial cancers showed some of the highest objective response rates to single-agent mTOR inhibitors, second only to lymphomas (71). Response rates in previously treated endometrial cancers were also encouraging (72). Most of these studies, however, included varied patient populations with endometrial cancers of different histologies and diverse numbers of prior cytotoxic or hormonal treatment regimens. Collectively, these studies showed response rates from 7% to 25%, with up to 57% of patients achieving stable disease, i.e., potential clinical benefit (71, 73). One study with a 20-week follow-up, limited to patients with endometrioid histology, showed a 21% stable disease rate at 20 weeks (74). A recent single-agent phase II study of temsirolimus showed a strong response (>80% stable disease) with long duration in chemotherapy-naive women with recurrent or metastatic endometrial cancer, compared with 50% in women with prior chemotherapy treatment (75). There was no correlation with PTEN status. These data suggest that we have a real opportunity to inhibit mTOR as a first-line treatment for endometrial cancer by using judicious combinations that capitalize on biologic synergies other than PTEN status and by exploiting combinations with other chemotherapeutics to maximize tumor cell killing and antiangiogenesis.

A significant untapped opportunity exists in the development of activity markers in the mTOR translational control pathway (76), focusing on highly mTOR-dependent oncogenic and survival mRNAs as biologic surrogate markers for treatment sensitivity and response. Clinical trials have produced conflicting results regarding whether mTOR or S6K phosphorylation (activity) correlates with treatment response, mirroring preclinical studies (71, 74). Clearly, there is a need to develop better biomarkers of mTOR sensitivity and endometrial cancer response, as well as treatment strategies that build on the molecular biologic understanding of selective translation inhibition by mTOR interference. Investigators need to reexamine the important issue of rapalog toxicity as currently configured in clinical use. It is unknown whether present levels of treatment efficacy will be maintained at lower dose levels. The fact that biologic exposure (i.e., plasma concentration over time) does not proportionally increase with dose may indicate that higher or more frequent dosing near the MTD merely increases toxicity, with little if any gain in antitumor activity and survival. A more fruitful approach might be to focus on achieving better synergy based on biologic activities with conventional chemotherapeutics, rather than on the MTD. In this regard, temsirolimus and everolimus are used at slightly lower levels than the MTD, whereas sirolimus is used at the MTD. Toxicities in clinical trials have included dyslipidemia, mucositis, myelosuppression, fatigue, infections, and pneumonitis. In a phase I trial of temsirolimus in combination with topotecan for advanced or recurrent gynecologic malignancies, the dose-limiting toxicity was myelosuppression, and the regimen was intolerable in women who had previously received radiation (77). Researchers have now completed or are conducting more than 10 early-phase clinical trials of rapalogs in patients with endometrial cancer to further investigate response, active combinations, and toxicities. The outcomes and biomarkers of these trials are being evaluated, and available results are summarized in Table 2. Overall, it is likely that intermittent rather than daily dosing will provide lower toxicity while preserving antitumor activity (34). These trials give investigators the ability to evaluate both retrospectively and prospectively treatment response with potential biomarkers based on translational control and translation targets of mTOR activity.
Table 2. Completed and ongoing phase I and II studies of mTOR inhibitors in endometrial cancer

<table>
<thead>
<tr>
<th>Study name</th>
<th>Summary</th>
<th>Status</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin–paclitaxel–ridaforolimus in endometrial, ovarian, and solids</td>
<td>Phase: IB</td>
<td>Approved, not yet active</td>
<td>N/A</td>
<td>N/A</td>
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<td></td>
<td>Assessment: MTD of ridaforolimus (rapalog) in combination with carboplatin–paclitaxel</td>
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<tr>
<td></td>
<td>Population: metastatic/recurrent endometrial cancer, up to 1 prior chemotherapy regimen</td>
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<tr>
<td>BEZ235 trial in patients with advanced endometrial carcinoma</td>
<td>Phase: II</td>
<td>Approved, not yet active</td>
<td>N/A</td>
<td>N/A</td>
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<td>Assessment: safety and activity of BEZ235 (dual P13K–mTOR inhibitor)</td>
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<td></td>
<td>Population: recurrent or progressive endometrial carcinoma after first-line treatment</td>
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<td>Study of the combination of temsirolimus and pegylated liposomal doxorubicin in advanced or recurrent breast, endometrial, and ovarian cancer</td>
<td>Phase: I</td>
<td>Active</td>
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<td>N/A</td>
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<tr>
<td></td>
<td>Assessment: combination of temsirolimus (rapalog) and PLD</td>
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<td></td>
<td>Population: advanced/recurrent breast, endometrial and ovarian cancer</td>
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<tr>
<td>Phase II study of Akt inhibitor MK2206 in patients with PIK3CA mutation recurrent or advanced endometrial carcinoma</td>
<td>Phase: II</td>
<td>Active</td>
<td>N/A</td>
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<td>Assessment: activity of MK2206 (Akt inhibitor)</td>
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<td></td>
<td>Population: recurrent/persistent endometrial cancer</td>
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<td>Study of weekly oral RAD001 in combination with oral topotecan in patients with advanced or recurrent endometrial cancer</td>
<td>Phase: I</td>
<td>Active</td>
<td>N/A</td>
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<td>Assessment: activity of topotecan and RAD001 (rapalog)</td>
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<td></td>
<td>Population: advanced/recurrent endometrial cancer</td>
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<td>BKM120 as second-line therapy for advanced endometrial cancer</td>
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<td>Active</td>
<td>N/A</td>
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<td>Assessment: activity of BKM120 (PI3K inhibitor)</td>
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<td></td>
<td>Population: recurrent endometrial cancer,</td>
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<td></td>
<td>Biomarkers: PI3K activation status</td>
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<td>Safety study of XL147 in combination with paclitaxel and carboplatin in adults with solid tumors</td>
<td>Phase: I</td>
<td>Active</td>
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<td>Assessment: safety and tolerability of XL147 (PI3K inhibitor)</td>
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<td></td>
<td>Population: solid tumors, including advanced/recurrent endometrial cancer</td>
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<td>Letrozole and RAD001 in advanced or recurrent endometrial cancer</td>
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<td></td>
<td>Assessment: activity and safety of RAD001 and Femara (letrozole)</td>
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<td></td>
<td>Population: recurrent/progressive endometrial cancer.</td>
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Table 2. Completed and ongoing phase I and II studies of mTOR inhibitors in endometrial cancer (Cont’d)

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<tr>
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</thead>
<tbody>
<tr>
<td>Phase II study of temsiroliimus and bevacizumab in patients with locally</td>
<td>Phase: II Assessment: tolerability and activity of temsiroliimus and bevacizumab (anti-VEGF antibody)&lt;br&gt;Population: multiple solid tumors</td>
<td>Active</td>
<td>N/A</td>
<td>N/A</td>
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<td>Molecular correlates associated with a phase II study of temsiroliimus</td>
<td>Phase: II Assessment: activity of temsiroliimus&lt;br&gt;Population: chemotherapy-naïve, recurrent/metastatic endometrial cancer</td>
<td>In progress</td>
<td>26% partial response, 63% stable disease; responses irrespective of PTEN status</td>
<td>Oza et al. (71)</td>
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<tr>
<td>Molecular correlates associated with a phase II study of temsiroliimus (CCI-779) in patients with metastatic or recurrent endometrial cancer (NCIC IND 160)</td>
<td>Biomarkers: PTEN status&lt;br&gt;Phase: II Assessment: response to AP23573 (ridaforolimus)&lt;br&gt;Population: progressive endometrial cancer, up to 2 prior chemotherapy regimens</td>
<td>In progress</td>
<td>33% stable disease, partial or complete response; 52% discontinued treatment before 4 cycles due to progression</td>
<td>Columbo et al. (73)</td>
</tr>
<tr>
<td>Phase II study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial cancer</td>
<td>Phase: II Assessment: response and toxicities of everolimus&lt;br&gt;Population: pretreated, recurrent, endometrioid endometrial cancer</td>
<td>Completed</td>
<td>No partial or complete responses; 21% stable disease at 20 weeks; 49% required dose reduction to half starting dose due to toxicity</td>
<td>Slomovitz et al. (74)</td>
</tr>
<tr>
<td>Phase I study of weekly temsiroliimus and topotecan in the treatment of advanced and/or recurrent gynecologic malignancies</td>
<td>Phase: I Assessment: tolerability of weekly topotecan with weekly temsiroliimus&lt;br&gt;Population: recurrent gynecologic malignancies not responsive to standard therapy</td>
<td>Completed</td>
<td>DLT for the combination was myelosuppression; patients with history of pelvic RT could not receive full doses of each agent in combination; 82% had stable disease at first evaluation</td>
<td>Temkin et al. (77)</td>
</tr>
<tr>
<td>Phase II study of temsiroliimus in women with recurrent or metastatic endometrial cancer; a trial of the NCIC group</td>
<td>Phase: II Assessment: response and toxicity of single-agent temsiroliimus&lt;br&gt;Population: chemotherapy-naïve or previously treated recurrent or metastatic endometrial cancer&lt;br&gt;Biomarkers: PTEN status</td>
<td>Completed</td>
<td>Naive patients: 14% partial response, 69% stable disease at 5 months and 9 months, respectively. Previously treated patients: 4% partial response, 48% stable disease at ~4 months. No correlation with PTEN status</td>
<td>Oza et al. (75)</td>
</tr>
</tbody>
</table>

Abbreviations: DLT, dose-limiting toxicity; N/A, not applicable; NCIC, National Cancer Institute of Canada; PLD, phospholipase D; RT, radiotherapy.
Future Directions: The Difficulty of Targeting mTOR and Translational Control

A significant problem in targeting mTOR with rapalogs is that these agents show partial inhibitory activity. They only moderately block mTORC1 and have little (if any) effect on mTORC2, thereby increasing AKT activity (37, 39, 40). It is unlikely that we can overcome this obstacle therapeutically by continuous rapalog exposure, which is reported to inhibit mTORC2 (78), because such an approach would require a dose that is not clinically sustainable. This issue may be obviated by the development of mTORC1/2 active-site catalytic kinase inhibitors that more strongly block S6K and 4E-BP phosphorylation and mTORC2 activity and consequent upregulation of AKT activity, and thus would likely provide greater therapeutic benefit. Preclinical studies in a murine B-cell lymphoma model suggest a particular synergy for tumor cell killing with mTORC1/2 inhibition in the setting of hyperactivated elf4E (79). This may be particularly relevant for the majority of endometrial cancers in which elf4E is overexpressed. On the other hand, preclinical and clinical trials to date have only begun to capitalize on the ability to synergize additional chemotherapies with partial mTORC1 inhibition, such as addition of ERK inhibitors. Further study of the rapalogs in combination with traditional cytotoxic agents, as well as the more-specific small-molecule mTOR kinase inhibitors, is therefore warranted.

Disclosure of Potential Conflicts of Interest

R.J. Schneider is a consultant to PTC Therapeutics, Inc., Celgene Corporation, and Eli Lilly/ImClone companies. S.V. Blank, J.P. Curin, S.B. Korets, and S. Czok disclosed no potential conflicts of interest.

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References


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