The PI3K/AKT/mTOR Pathway as a Therapeutic Target in Endometrial Cancer

Brian M. Slomovitz and Robert L. Coleman

Abstract

Endometrial cancer is the most common gynecologic malignancy in the United States. Overactivation of the PI3K/AKT/mTOR pathway, a signaling pathway that plays an important role in cellular growth and survival, has recently been implicated in endometrial cancer pathogenesis, and as such, inhibition of the PI3K/AKT/mTOR pathway is of therapeutic interest. Preclinical and clinical studies are proving useful in elucidating the antitumor effects of different PI3K/AKT/mTOR pathway inhibitors, and in defining which patient populations these inhibitors might be most effective in. For example, an increasing amount of preclinical data suggest that loss of PTEN or genetic alteration of PI3KCA may be indicators of sensitivity to PI3K/AKT/mTOR pathway inhibition, while activating KRAS mutations may predict resistance. In the latter case, combined inhibition of the RAS/RAF/MEK and PI3K/AKT/mTOR pathways has been suggested as a therapeutic strategy. In addition, the PI3K/AKT/mTOR pathway has been implicated in conferring resistance to conventional therapies, and so PI3K/AKT/mTOR pathway inhibitors in combination with hormonal and/or cytotoxic agents are being evaluated. In conclusion, preclinical models are providing insights into the antitumor activity of PI3K/AKT/mTOR pathway inhibition, and are helping define patient populations most likely to benefit from these therapies. Clinical validation of these findings is ongoing.

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States. In 2012, endometrial cancer is expected to be diagnosed in 47,130 patients and account for just more than 8,000 deaths in the United States (1). In the majority (72%) of cases (2), endometrial cancers are detected early, and are successfully treated with surgery and/or radiotherapy. However, for patients with advanced or recurrent disease, or for those who wish to preserve their fertility, limited treatment options are available.

Clinical, pathologic, and molecular data suggest that endometrial cancer may be broadly categorized into 2 subgroups. "Type I" carcinomas, or endometrioid endometrial cancers, account for 70% to 80% of endometrial cancers. The majority are low grade, are of endometrioid histology, are commonly driven by excessive estrogen, and are characterized by PTEN loss and mutations in PIK3CA, KRAS, and β-catenin, along with microsatellite instability (3, 4). Diagnosed early, the prognosis for type I endometrial cancer is favorable, with 5-year survival rates of more than 97% and more than 80% in stage I and stage II, respectively (5). "Type II" carcinomas, or nonendometrioid endometrial cancers, account for 10% to 20% of endometrial cancers. They are most commonly of serous and clear-cell morphology, are estrogen independent, and are often characterized by genetic alteration in p53, HER2/neu, p16, and E-cadherin (3, 4). Type II endometrial cancers usually have a poorer prognosis than type I endometrial cancers, and, although less common, account for 44% of endometrial cancer-related deaths (6). Despite being an important general predictor of clinical behavior, the type I/type II classification system fails to predict which endometrioid tumors are likely to recur, undergo deep myometrial invasion, and metastasize. Recent molecular profiling has shown that increased PI3K/AKT/mTOR signaling is associated with aggressive disease and poor prognosis, irrespective of endometrial cancer tumor type (7).

Acknowledgment of the key role played by the PI3K/AKT/mTOR pathway in endometrial cancer has led to its vigorous pursuit as a target for rational drug design. The following reviews the role of the PI3K/AKT/mTOR pathway and its alteration in endometrial cancer, and discusses how the pathway might best be targeted in light of ongoing preclinical and clinical trials.

The PI3K/AKT/mTOR Pathway in Endometrial Carcinoma

There are 3 classes of PI3Ks with distinct structure, substrate specificity, and lipid products. Class IA PI3Ks are the most studied, and are widely implicated in cancer. They are...
heterodimers, and comprise regulatory p85 and catalytic p110 subunits. Class IA PI3K is activated by receptor tyrosine kinases (RTK), G protein-coupled receptors, and some oncogenes (e.g., RAS). Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2] and converts it into phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3]. PI(3,4,5)P3 binds to the pleckstrin homology domain of proteins such as PDK1 and AKT and recruits them to the plasma membrane. This process is negatively regulated by the tumor suppressors PTEN and INPP4B, which convert PI(3,4,5)P3 back to PI(4,5)P2, and PI(3,4)P2 back to PI(3)P, respectively. Once at the plasma membrane, AKT is activated through the phosphorylation of its serine and threonine residues at positions 308 and 473, respectively. Activated AKT initiates a cascade of downstream signaling events, which promote cellular growth, metabolism, proliferation, survival, migration, apoptosis, and angiogenesis. A major downstream effector of AKT is mTOR complex 1 (mTORC1); its downstream targets control protein synthesis. Another mTOR complex, mTORC2, participates in the activation of AKT through the phosphorylation of Ser473 (8, 9).

The PI3K/AKT/mTOR pathway is also involved in cross-talk with other signaling pathways, including the RAS/RAF/MEK (10) and estrogen receptor (ER) pathways (11; Fig. 1).

Alteration of the PI3K/AKT/mTOR pathway in endometrial carcinoma

Genetic alterations leading to increased PI3K/AKT/mTOR signaling are widespread in both type I and type II...
endometrial cancer (Table 1; 12–24). *PTEN* is the most commonly altered gene in type I endometrial cancer, is frequently mutated in type II endometrial cancer (12), and is also commonly observed in endometrial hyperplasias with or without atypia, suggesting *PTEN* mutations are an early event in type I endometrial transformation (25). *PIK3CA* (13, 14), which encodes p110α, the main catalytic subunit of PI3K involved in cancer, and *PIK3R1* (14, 15), which encodes p85α, the regulatory subunit of PI3K, are also commonly mutated in endometrial cancer, and *PIK3CA* is frequently comutated with *PTEN*. *AKT* mutations have also been described, albeit in only 2% of type I endometrial cancer (16). Alterations in RTKs are also frequent in endometrial cancer and include amplification/overexpression of HER2 (17, 18), mutation of fibroblast growth factor receptor 2 (FGFR2; 19, 20), overexpression of EGFR receptor (EGFR; 21, 22), and overexpression of insulin-like growth factor receptor 1 in complex, atypical hyperplasia, and in type I endometrial cancer (26). Activating mutations in *KRAS* have also been described, predominantly in type I endometrial cancer (23, 24), and directly activate the p110 subunit of PI3K (10). In addition, loss of heterozygosity of *INPP4B* has been observed in breast (particularly basal-like and those with *BRCA1* mutation) and ovarian cancers, where it associates with decreased survival (27). However, currently a role in endometrial cancer is unconfirmed.

### Inhibitors of the PI3K/AKT/mTOR Pathway

PI3K/AKT/mTOR pathway inhibitors fall into 4 main categories: mTOR inhibitors, PI3K inhibitors, dual mTOR/PI3K inhibitors, and AKT inhibitors (Fig. 2). In addition, the antidiabetes drug metformin also inhibits the PI3K/AKT/mTOR pathway via activation of the AMP protein kinase (AMPK) pathway. mTOR inhibitors either inhibit mTORC1 only, or are dual mTORC1/2 inhibitors. mTORC1 inhibitors currently in clinical development include everolimus, temsirolimus, and ridaforolimus. Recently, everolimus and temsirolimus showed antitumor activity in endometrial cancer cell lines, with greatest sensitivity in cells with *PIK3CA* and/or *PTEN* mutations (28–30). Furthermore, everolimus reduced progression of endometrial hyperplasia in a *PTEN* heterozygous mouse model (31), and repressed tumor growth in mouse xenograft models harboring endometrial cancer cells with loss of *PTEN* and/or *PIK3CA* mutations (32). Consistent with these findings, ridaforolimus also showed antitumor activity in endometrial cancer cells and a mouse xenograft model, with greatest sensitivity observed in cells with loss of *PTEN* or increased phosphorylated or total AKT (33). In patients with recurrent and/or metastatic endometrial cancer, single-agent treatment with everolimus, temsirolimus, and ridaforolimus has led to clinical benefit rates of 21% (34), 52% to 83% (35), and 33% to 66% (36, 37), respectively. For both temsirolimus and ridaforolimus, the best responses were seen in patients with no prior chemotherapy (35, 37). Furthermore, ridaforolimus was also shown to significantly improve progression-free survival (PFS) in patients with no further approved treatment options (38). Common adverse events in these studies included fatigue, nausea, mucositis, diarrhea, and rash. Hypertriglycerideremia was also reported in 2 studies (34, 38), and pneumonitis was common in 1 study (37%). In addition, hyperglycemia, a possible “on target” effect of PI3K/AKT/mTOR pathway inhibition, was observed in 2 studies (27% and 19%, respectively; 34, 38). A possible caveat to the use of inhibitors that target mTORC1 only is the potential loss of negative regulation on PI3K/AKT/mTOR pathway activity (Fig. 1; 39, 40). In light of this, second-generation mTOR inhibitors that target the catalytic sites of both mTORC1 and mTORC2 have been developed. In preclinical studies, the mTORC1/2 inhibitors AZD8055 and OSI-027 resulted in dose-dependent growth inhibition in a variety of cell lines and xenograft models including endometrial cancer models (41, 43). AZD8055, OSI-027, and INK128 are currently in early-stage clinical trials in solid tumors, including endometrial cancer.

### PI3K inhibitors

PI3K inhibitors are either pan-PI3K inhibitors, which inhibit all 4 Class I PI3Ks, or isoform-selective PI3K inhibitors. In preclinical studies, the pan-PI3K inhibitors GDC-0941 and NVP-BKM120 inhibited cancer cell growth in a variety of cell lines, with NVP-BKM120 demonstrating particular activity in cells with *PIK3CA* mutations (44, 45). In addition, GDC-0941 halted tumor progression in xenograft mice harboring an FGFR2-mutant endometrial cancer cell line (46). GDC-0941, NVP-BKM120, and XL147 are all in phase I/II clinical trials in patients with advanced solid tumors, while phase II trials of NVP-BKM120 and XL147 are ongoing in endometrial cancer. In these early trials, frequent adverse events included nausea, fatigue,

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**Table 1. Incidence of genetic alterations in type I and II endometrial carcinomas**

<table>
<thead>
<tr>
<th>Gene (reference)</th>
<th>Incidence of genetic aberrations in endometrial cancer, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type I</td>
</tr>
<tr>
<td>PTEN (12)</td>
<td></td>
</tr>
<tr>
<td>Sequence abnormalities</td>
<td>70</td>
</tr>
<tr>
<td>Protein loss</td>
<td>75</td>
</tr>
<tr>
<td>PIK3CA (13, 14)</td>
<td>41–52</td>
</tr>
<tr>
<td>PIK3R1 (14, 15)</td>
<td>21–43</td>
</tr>
<tr>
<td>AKT1 (16)</td>
<td>2</td>
</tr>
<tr>
<td>RTKs</td>
<td></td>
</tr>
<tr>
<td>HER2 amplification (17)</td>
<td>3</td>
</tr>
<tr>
<td>HER2 overexpression (17, 18)</td>
<td>8</td>
</tr>
<tr>
<td>FGFR (19, 20)</td>
<td>12–16</td>
</tr>
<tr>
<td>EGFR overexpression (21, 22)</td>
<td>~50–80</td>
</tr>
<tr>
<td>KRAS (23, 24)</td>
<td>13–26</td>
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vomiting, and rash (47–49). Manageable hyperglycemia has also been noted in patients treated with NVP-BKM120 (47).

An alternative strategy being evaluated is targeting the specific PI3K p110 isoforms involved in a particular cancer, which, because of the important and differing roles of the p110 subunits, has the theoretical advantage of an improved side effect profile. p110α-selective inhibitors, such as INK1117 and NVP-BYL719, have shown preclinical activity in tumor cell lines with PIK3CA mutations (50, 51), and are currently in early-phase clinical trials. The activity of INK1117, however, is much lower in PTEN-deficient tumor cells (51), which are reliant on p110β for PI3K signaling (52). To this end, p110β inhibitors such as GSK2636771, and dual inhibitors of p110α and p110β are in early-stage clinical development. Given the high prevalence of both PTEN deficiency and PIK3CA mutation in endometrial cancer, it seems likely that the success of isoform-specific inhibitors in endometrial cancer will be dependent on the determination of the PIK3CA and PTEN (and possibly INPP4B) status of individual tumors.

Dual mTOR/PI3K inhibitors

Dual mTOR/PI3K inhibitors competitively bind the ATP-binding cleft of both Class I PI3Ks and mTORC1/2, and should lead to more complete suppression of the PI3K/AKT/mTOR pathway than targeting either component independently.

In preclinical trials, GDC-0980 and NVP-BEZ235 reduced cell growth in several cancer cell lines and tumor xenograft models (53, 54). Greatest sensitivity to NVP-BEZ235 was observed in endometrial cancer cells with PIK3CA and/or PTEN mutations (28, 29). In addition, NVP-BEZ35 significantly suppressed tumor growth in mice inoculated with the endometrial cell lines AN3CA or Hec-59, which contain PTEN and PIK3CA mutations, respectively. Surprisingly, however, in vivo results with NVP-BEZ235 were similar to, but not better than, those seen with everolimus (32). Phase I clinical trials of GDC-0980 and NVP-BEZ235 have shown antitumor activity in advanced solid tumors (55, 56). A phase I study of XL765 in patients with advanced solid tumors and a phase II study of GDC-0980 in patients with recurrent or persistent endometrial cancer are also ongoing. To date, the safety profile of these inhibitors has been similar to that of pan-PI3K inhibitors, with common adverse events including nausea, diarrhea, fatigue, and vomiting (55–57).

AKT inhibitors

Although AKT mutations are extremely rare (16), increased AKT signaling is commonly observed in endometrial cancer. AKT inhibitors either compete for the ATP-binding site, or inhibit AKT allosterically. A potential caveat to targeting AKT, however, is that inhibition may lead to increased compensatory signaling through AKT-independent PI3K effectors, and that loss of negative inhibition of
AKT on its downstream targets may also have detrimental effects. Indeed, the AKT-independent effector of PI3K signaling, SGK3, was shown to promote cancer in the presence of PIK3CA mutations (58). Despite these concerns, the allosteric AKT inhibitors perifosine and MK2206 showed antitumor activity in preclinical investigations in various cancer cell lines, including endometrial cancer cells (59, 60). Indeed, perifosine induced apoptosis in human endometrial cancer cell lines under estrogen-reduced conditions, and was more effective than both everolimus and the EGFR inhibitor gefitinib (59). However, the results of a phase II trial in soft-tissue sarcomas were less encouraging, with little anti-tumor activity observed (61). Early-stage clinical trials of MK2206 and the competitive AKT inhibitors, ARQ 092, AZD5363, GDC-0068, and GSK2141795, are ongoing in advanced solid tumors, while MK2206 is also being investigated in a phase II trial in endometrial cancer.

Metformin

Diabetes is a major risk factor for the development of several cancers. Recently, however, the use of the antidiabetes drug metformin was shown to reduce the incidence of malignancies in patients with diabetes (62). The mechanism of action of metformin in this regard has been linked to regulation of PI3K/AKT/mTOR signaling via its activation of AMPK. AMPK regulates PI3K/AKT/mTOR signaling by inhibiting insulin receptor substrate 1 (64). The clinical activity of metformin is now being investigated in several cancers, including endometrial cancer.

Combining PI3K/AKT/mTOR Inhibition with Other Therapies

A limitation to the use of PI3K/AKT/mTOR pathway inhibitors in endometrial cancer will likely be the presence of numerous signaling feedback loops and cross-talk between signaling pathways. Combining PI3K/AKT/mTOR pathway inhibitors with other therapies might improve efficacy.

Activation of RTKs stimulates both the PI3K/AKT/mTOR and RAS/RAF/MEK signaling pathways, and evidence suggests that inhibition of both pathways may be more effective than targeting either alone (65, 66). Indeed, although the PI3K inhibitor GDC-0941 halted tumor growth in xenograft mice harboring EGFR-mutant endometrial cancer cells, only the combination of GDC-0941 with the MEK inhibitor PD0325901 led to robust tumor shrinkage (46). Furthermore, both in vitro and in vivo data have shown that KRAS-mutant cancer cells are not sensitive to treatment with PI3K/AKT/mTOR pathway inhibitors alone (65, 67). Indeed, in endometrial cancer cell lines, KRAS mutations segregated with reduced sensitivity to everolimus and to NVP-BEZ235. Combination of NVP-BEZ235 with the MEK inhibitor PD98059, however, synergistically suppressed proliferation in endometrial cancer cell lines with PTEN and KRAS mutations (28). Contrary to these in vitro studies, a phase II clinical trial in 28 patients with endometrial cancer found no correlation between KRAS mutations and response to everolimus (68). Subgroup patient numbers in this study, however, were low, and response was defined as clinical benefit, rather than an objective response. Additional, larger studies are needed to confirm the importance of KRAS mutations with respect to response to PI3K/AKT/mTOR pathway inhibitors in endometrial cancer.

Given the importance of ER signaling in type I endometrial cancer, and the cross-regulation between the ER and PI3K/AKT/mTOR pathways, combining agents that disrupt ER signaling with PI3K/AKT/mTOR pathway inhibitors may also result in synergistic antitumor responses. Indeed, the aromatase inhibitor letrozole in combination with everolimus, showed enhanced activity in a phase II clinical trial in advanced endometrial cancer (69). Meanwhile, the combination of everolimus with the aromatase inhibitor exemestane significantly improved PFS in patients with aromatase inhibitor-refractory breast cancer (70), thus demonstrating proof-of-concept that PI3K/AKT/mTOR pathway inhibitors may reverse resistance to aromatase inhibitors.

Progestins are a common treatment for young women with early-stage endometrial cancer who wish to preserve their fertility. Although treatment with progestins has proven effective in both early- and advanced-stage disease, many patients are insensitive to treatment or develop resistance (71, 72). Resistance to progestins has been shown to result from reduced progesterone receptor expression (73), which, in turn, results from overexpression of EGFR (74), suggesting that pathways downstream of EGFR may be involved in resistance development. Inhibition of the PI3K/AKT/mTOR pathway with the mTORC1 inhibitor LY294002 resulted in the upregulation of progesterone receptor expression, diminished cell growth in progesterin-resistant endometrial cancer cells, and reversed resistance to progestins in endometrial cancer xenograft mice (73). In the clinical setting, however, a trial of temsirolimus in combination with alternating 3-week cycles of megestrol acetate (a progesterone derivative) and tamoxifen in patients with advanced, recurrent, or persistent endometrial cancer was discontinued because of excess venous thrombosis (75). It remains to be determined whether the combination of progestins with PI3K/AKT/mTOR inhibitors would be better tolerated and effective at earlier stages of the disease.

Activation of the PI3K/AKT/mTOR pathway has also been implicated as a mechanism of resistance to standard cytotoxic agents in endometrial cancer (76, 77), and combining these agents with PI3K/AKT/mTOR pathway inhibitors has resulted in improved efficacy in numerous model systems (44), including endometrial cancer models (78). In a phase I trial of temsirolimus in combination with carboplatin and paclitaxel in advanced solid tumors, 9 of 11 patients (82%) with endometrial cancer achieved objective partial responses (79). A randomized, 3-arm, phase II trial (NC10977574) is now evaluating this combination in patients with advanced or recurrent endometrial cancer who have received no prior chemotherapy or targeted therapy.
RTK inhibitors targeting EGFR, EGFR/HER2, and VEGF are currently in phase I/II clinical trials in endometrial cancer. Resistance to such agents, however, is often reported in other cancer types and has been shown to be a result of hyperactivation of the PI3K/AKT/mTOR pathway (80, 81). If approved in endometrial cancer, evaluation of the potential of PI3K/AKT/mTOR pathway inhibitors to restore sensitivity to these agents in refractory patients is warranted.

Finally, because PTEN appears to also play a role in homologous recombination, mutation, or loss of expression of PTEN may provide a “contextual” synthetic lethality in the tumor microenvironment, and thus enhance PARP inhibitor-mediated cytotoxicity (82, 83). Currently, a trial combining the PARP inhibitor olaparib with NVP-BKM120 is initiating accrual.

Future Research
Although PI3K/AKT/mTOR pathway inhibitors have shown anticancer activity in preclinical models of endometrial cancer, several questions remain to be addressed in clinical trials. For example, will dual targeting of PI3K and mTORC1/2 have a more profound effect than inhibiting PI3K alone? Will isoform-selective inhibition of PI3K be better tolerated than pan-PI3K inhibition? Which are the most appropriate combination partners for use in patients with endometrial cancer? Finally, should patients be selected for clinical trials based on molecular profiling, and, if so, what biomarkers should be used?

Patient selection for clinical trials
Robust preclinical data have suggested that PI3K/AKT/mTOR pathway inhibition may be most effective in patients with activating mutations in PIK3CA and/or loss of PTEN, while activating mutations in KRAS are likely to predict resistance, but clinical data are needed to support this. A recent retrospective phase I clinical trial in patients with gynecologic and breast malignancies reported significantly higher response rates in tumors with PIK3CA mutations (30%) compared with non-PIK3CA mutated tumors (10%) treated with PI3K/AKT/mTOR pathway inhibitors either as single agents or in combination with other therapies. When considering patients with endometrial cancer only, this response rate was 33% (84). Although these data suggest PIK3CA mutations may be predictive of response, only 6 patients with endometrial cancer and PIK3CA mutations were evaluable for response, and further prospective clinical trials with each individual PI3K/AKT/mTOR pathway inhibitor, either alone or in combination with other agents, are required to conclude about the predictive nature of PIK3CA mutations. In addition, the role of other biomarkers, such as loss of PTEN or levels of phosphorylated AKT or S6K should also be addressed in the clinic. As long as the predictive nature of these biomarkers remains unknown, all patients with endometrial cancer, regardless of PI3K/AKT/mTOR activation status, should be enrolled into clinical trials, and tumor samples for determination of PI3K/AKT/mTOR pathway activation status collected. With this in mind, a phase II clinical trial of the PI3K inhibitor NVP-BKM120 (NCT01289041) is recruiting patients to look at the relationship between PI3K/AKT/mTOR pathway activation status and response to treatment in advanced endometrial cancer. Meanwhile, a phase II trial of the AKT inhibitor MK-2206 (NCT01312753) is recruiting to further assess the role of PIK3CA mutations in predicting response in advanced and recurrent endometrial cancer. Results of these trials will help guide decisions about patient selection for future endometrial cancer trials of PI3K/AKT/mTOR pathway inhibitors.

PI3K/AKT/mTOR pathway inhibitors in endometrial cancer prevention
Because metformin reduces the incidence of malignancies in patients with diabetes, and there are a large number of known risk factors for endometrial cancer (e.g., diabetes, obesity, Lynch syndrome, tamoxifen use), as well as an identifiable precursor of endometrial cancer (complex hyperplasia with atypia), there is a possibility that PI3K/AKT/mTOR pathway inhibitors could be used in endometrial cancer prevention. Encouragingly, everolimus prevented tamoxifen-associated and estrogen-related endometrial hyperplasia in mice (85). Prospective clinical trials in at-risk patients will be required to show the feasibility of this approach.

Conclusions
Alteration of the PI3K/AKT/mTOR pathway is heavily implicated in endometrial cancer pathogenesis, and targeting the effectors of this pathway is a rational therapeutic approach. Inhibitors of the PI3K/AKT/mTOR pathway are currently in mid- and late-stage trials in endometrial cancer, as single agents and in combination with other therapies. Preclinical data are useful to understand how these inhibitors might most effectively be used in patients with endometrial cancer, and which populations will most likely respond. Conclusions from preclinical studies, however, will also require clinical validation. Finally, a key challenge for PI3K/AKT/mTOR pathway inhibition will likely be the level of cross-talk and negative feedback along parallel pathways. Preclinical data suggest that some difficulties may be overcome by combining PI3K/AKT/mTOR pathway inhibitors with therapies targeting other pathways. Clinical validation of these findings is required.
Writing, review, and/or revision of the manuscript: B.M. Slomovitz, R. Coleman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.M. Slomovitz, R. Coleman

Acknowledgments
The authors thank Amanda Quinn for her medical editorial assistance with this manuscript.

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