New Strategies in Endometrial Cancer: Targeting the PI3K/mTOR Pathway—The Devil Is in the Details

Andrea P. Myers

Abstract

Endometrial cancer is the most common gynecologic malignancy in the developed world and affects approximately 40,000 women in the United States each year. The phosphoinositide 3-kinase (PI3K) signaling pathway regulates key aspects of cancer biology including glucose uptake and metabolism, cellular growth, and survival. Endometrial cancers harbor the highest rates of PI3K pathway alterations reported to date. The PI3K pathway is highly druggable and several classes of agents are in clinical development including rapalogs, pan-PI3K inhibitors, PI3K isoform-specific inhibitors, dual PI3K/mTOR catalytic inhibitors, mTOR-specific catalytic inhibitors, and AKT inhibitors. It has been 10 years since the initiation of the first studies of rapalogs as anticancer agents. There are more than 20 registered clinical trials of PI3K/mTOR inhibitors as single agents or in therapeutic combinations for the treatment of endometrial cancers. What have we learned from the completed studies? What can we expect to learn from ongoing studies? What should we anticipate moving forward? Clin Cancer Res; 19(19); 5264–74. ©2013 AACR.

Background

Endometrial cancer

Endometrial cancer is the most common gynecologic malignancy in the developed world and affects approximately 40,000 women in the United States each year (1, 2). Endometrial cancer is increasing in incidence, likely due to the growing epidemic of obesity, a strong risk factor for endometrial cancer (2–4). Although the majority of endometrial cancers are diagnosed when localized to the uterus, up to 25% of cases recur. Systemic therapies are limited in efficacy for recurrent and metastatic disease and new therapies are in need (5).

PI3K signaling

The phosphoinositide 3-kinase (PI3K) pathway (Fig. 1) regulates key aspects of cancer biology including metabolism, cellular growth, and survival (6). Upon stimulation of receptor tyrosine kinases (RTK), PI3K phosphorylates the lipid phosphatidylinositol 4,5-biphosphate (PIP2), creating phosphatidylinositol 3,4,5-triphosphate (PIP3) (7). PIP3 recruits pleckstrin homology domain-containing proteins, including the protein kinase AKT, to the membrane. AKT is phosphorylated and activated by mTOR complex 2 (mTORC2) and 3-phosphoinositide-dependent protein kinase 1 (PDK1; ref. 8). Among its targets, AKT phosphorylates and inhibits tuberous sclerosis complex 2 (TSC2) within the multiprotein TSC complex, which indirectly inhibits mTOR complex 1 (mTORC1). Hence, PI3K-AKT signaling activates mTORC1, a key regulator of metabolism and biosynthetic processes (9, 10). PTEN hydrolyzes PIP3 back to PIP2, deactivating the pathway (11, 12). The PI3K pathway contains numerous negative feedback loops and is intricately networked with other signaling pathways including the RAS–ERK pathway. Signals from both AMP-activated protein kinase (AMPK), a sensor of energy stress, and estrogens are also integrated into PI3K signaling (13–16).

PI3K in endometrial cancer

Endometrial cancers harbor the highest rates of PI3K pathway alterations reported to date (17). The importance of the PI3K pathway in endometrial cancers was underscored by the identification of germline mutations in PTEN as the etiology of Cowden syndrome, an inherited cancer syndrome for which endometrial cancer is a diagnostic criterion (18, 19). High...
rates of somatic PTEN mutations were reported in sporadic cases of endometrial cancers shortly thereafter and genetically engineered mouse models confirmed the role of PTEN loss in endometrial cancer development (20–24). Candidate gene approaches identified high rates of PIK3CA (25%–40%) and PIK3R1 (15%–25%) mutations, which encode the catalytic and regulatory subunits of the PI3K holoenzyme (25–27). Recently completed high-throughput mutation detection as well as whole exome sequencing studies have confirmed these reports and have identified mutations in other key PI3K pathway members (Fig. 1; refs. 17, 28).

Targeting PI3K
The PI3K pathway is highly druggable and several classes of agents are in clinical development (Fig. 2). The rapamycin analogs (rapalogs) directly bind and
allosterically inhibit mTORC1. Although they target downstream of PI3K they are often introduced as the first clinical PI3K pathway inhibitors. Indeed, nearly 20 years of laboratory, translational, and clinical experience with the rapalogs has offered great insight into basic PI3K signaling as well as potential pitfalls and challenges for clinical developing of these inhibitors as anticancer agents (29). Newer classes of PI3K pathway inhibitors in clinical development include pan-PI3K inhibitors, PI3K isoform-specific inhibitors, dual PI3K/mTOR catalytic inhibitors, mTOR-specific catalytic inhibitors, and Akt inhibitors (30, 31).

On the Horizon

Given the high rate of PI3K pathway alteration, endometrial cancer seems to be an optimal disease for the development of PI3K pathway inhibitors.
It has been 15 years since the initiation of the first studies of rapalogs as anticancer agents. There are numerous registered clinical trials of PI3K/mTOR inhibitors as single agents or in combinations for the treatment of endometrial cancers (Tables 1 and 2). What have we learned from the completed studies? What can we expect to learn from ongoing studies? What should we anticipate moving forward?

The rapalogs

Rapalogs as single agents. From more than a half dozen clinical trials of the rapalogs as single agents, it can be concluded that rapalogs have a modest, but reproducible antitumor activity in endometrial cancer (Table 1). Objective response rates range from 0%–30% depending upon the clinical population; clinical response rates are higher in populations that have not received prior chemotherapy and response occurs across histologic subtypes including endometroid, high-grade papillary serous, and clear cell cancers. Importantly, there is a subset, albeit small, of patients with complete and/or durable responses (32–37).

Predictive biomarkers for rapalogs. A molecular biomarker that predicts the clinical benefit of rapalogs has yet to be identified for endometrial cancer. Several studies have explored the association of molecular biomarkers and response (33, 38–40). The largest, most comprehensive study to date has been a combined analysis of three National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) studies, each of which evaluated a rapalog as single-agent therapy in advanced endometrial cancer (40). Seventy to eighty tumor samples were evaluated for common mutations in a set of 17 related cancer genes as well as for protein expression of PTEN and stathmin (STMN), a cytoskeletal protein with expression that is associated with PI3K pathway activation (41). These studies reported no association between clinical response rates and PTEN mutation, PIK3CA mutation, PTEN or STMN protein expression.

The strength of these studies is the large sample size. Although the studies were exploratory in nature, given the rates of the PTEN mutations and protein loss, PIK3CA mutation and STMN expression in endometrial cancer, there was adequate power to detect clinically meaningful differences in outcomes of the defined molecular subgroups. There were also weaknesses in this study. First, the study population is clinically heterogeneous and includes untreated and pretreated patients and patients who were treated with different rapalogs. Second, although technologically advanced for the time, the mutation analysis was limited to “hotspots” and thus misclassification may have been introduced (26). Finally, associative analyses were limited to objective response rates and did not include time to event studies.

Associative studies from the Group d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) led study of everolimus were recently reported (38). In a study of 34 patients, there was no identified association of PTEN or PIK3CA mutation and clinical benefit. However, K-Ras mutation was associated with a decreased progression-free and overall survival in this population.

Although imperfect and validation from other larger studies is needed, these data suggest that PTEN and PIK3CA alterations are not reliable biomarkers for predicting clinical benefit to the rapalogs and that K-Ras mutation may predict a group unlikely to benefit from rapalogs. Indeed, these results are consistent with preclinical and translational data which highlight potential clinical pitfalls of the rapalogs as single agents. Rapalog exposure relieves mTORC1-dependent negative feedback loops affecting RTK signaling resulting in upregulation of both RAS-ERK and PI3K pathways (13). Tumors can thus circumvent rapalog inhibition by relying on RAS-ERK signaling or PI3K signals that are independent of mTORC1.

Other candidate biomarkers. Although not yet molecularly defined, there remains a subset of patients who greatly benefit from rapalog monotherapy. The clinical use of prospectively classifying these patients mandates that we continue the search for a predictive biomarker. Recent clinical data on rapalogs in other cancers as well as laboratory studies of mTOR signaling suggest additional avenues to explore.

In bladder cancer, TSC1 mutation is associated with clinical response to a rapalog (42). Iyer and colleagues conducted whole genome sequencing on archived tumor from a patient who had a complete and durable response to everolimus. Analysis revealed mutations in TSC1 and neurofibromin 2 (NF2), genes whose protein products regulate mTORC1 signaling. Targeted sequencing of the tumors from the other trial participants identified an association with TSC1 mutation and best tumor response. These data suggest that TSC1 and NF2 be evaluated as biomarkers for rapalogs in endometrial cancer and also highlight the benefit of deep sequencing exploration of tumors from patients with an unexpected level and duration of benefit to molecularly targeted drugs.

The perspective that mTORC1 functions only to relay proliferative signals from PI3K is a limited view of mTORC1 regulation and function. Recent laboratory-based studies highlight that our understanding of mTORC1 is incomplete. In addition to signals from the TSC complex, mTORC1 is directly regulated by other nutrient-sensing proteins including the recently described regulator complex (43). In addition, two research groups have identified the importance of mTORC1 in regulating de novo pyrimidine synthesis by its phosphorylation and activation of the enzyme CAD (carbamoylphosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; refs. 44, 45). Tumors with microsatellite instability have been reported to have CAD amplification, perhaps suggesting a heavy reliance on de novo pyrimidine synthesis.
Table 1. Completed and ongoing phase II clinical trials of single agent PI3K/mTOR pathway inhibitors in endometrial cancer

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Target</th>
<th>Treatment population</th>
<th>NCT # (date registered)</th>
<th>Clinical results (n)</th>
<th>Toxicities</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus</td>
<td>mTORC1</td>
<td>Chemo-naive</td>
<td>NCT00072176 (11/2003)</td>
<td>CR (0/33)^</td>
<td>Most common ≥ grade 3 AEs: fatigue, diarrhea, pneumonitis</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (4/33)^</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks^c (20/33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTORC1</td>
<td>1 prior line</td>
<td>NCT00072176 (11/2003)</td>
<td>CR (0/27)</td>
<td>Most common ≥ grade 3 AEs: fatigue, diarrhea, pneumonitis, dyspnea, hypokalemia</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (1/27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks^c (12/27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTORC1</td>
<td>1-2 prior lines^d</td>
<td>NCT00087685 (7/2004)</td>
<td>CR (0/35)</td>
<td>Most common ≥ grade 3 AEs: fatigue, nausea lymphopenia, anemia, hyperglycemia</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (0/35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks (12/35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>mTORC1</td>
<td>1-2 prior lines</td>
<td>NCT00122343 (7/2005)</td>
<td>CR (0/45)</td>
<td>Most common ≥ grade 3 AEs: anemia, hyperglycemia, mouth sores</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (5/45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 16 weeks (8/45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>mTORC1</td>
<td>Adjuvant only</td>
<td>NCT00770185 (10/2008)</td>
<td>CR (0/35)</td>
<td>Most common ≥ grade 3 AEs: lymphopenia, anemia</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (2/35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks^c (15/35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridaforolimus (vs. progestins)</td>
<td>mTORC1</td>
<td>1-2 lines</td>
<td>NCT00739830 (8/2010)</td>
<td>CR (0/64)^</td>
<td>Most common ≥ grade 3 AEs: anemia, hyperglycemia, back pain, asthenia</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (0/64)^</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks^c (22/64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>median PFS 3.6 vs. 1.9 months (ridaforolimus vs. progestins)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTORC1</td>
<td>1-2 prior lines</td>
<td>NCT00870337 (3/2009)</td>
<td>CR (0/44)</td>
<td>Most Common ≥ grade 3 AEs: fatigue, anorexia, infection, diarrhea, lymphopenia, anemia, thromboembolic event, hyperglycemia</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (4/44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 12 weeks (14/44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR245408</td>
<td>Pan-PI3K</td>
<td>1-2 prior lines</td>
<td>NCT01013324 (11/2009)</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
<td>Completed, not reported</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Completed and ongoing phase II clinical trials of single agent PI3K/mTOR pathway inhibitors in endometrial cancer (Cont’d)

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Target</th>
<th>Treatment population</th>
<th>NCT # (date registered)</th>
<th>Clinical results (n)</th>
<th>Toxicities</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-2206</td>
<td>AKT</td>
<td>1-2 prior lines</td>
<td>NCT01312753 (12/2010)</td>
<td>CR (0/36)</td>
<td>Not recruiting, not reported</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PR (2/36)</td>
<td>Not recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD ≥ 8 weeks (12/36)</td>
<td>Not recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS ≥ 6 months (4/36)</td>
<td>Not recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td>NVP-BKM120</td>
<td>Pan-PI3K</td>
<td>Adjuvant only</td>
<td>NCT01289041 (1/2011)</td>
<td>Not yet reported</td>
<td>Recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td>GDC-0980</td>
<td>Dual mTORC/PI3K</td>
<td>1-2 prior lines</td>
<td>NCT0101455 (10/2011)</td>
<td>Not yet reported</td>
<td>Recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td>PF-05212384</td>
<td>Dual mTORC/PI3K</td>
<td>1-2 prior lines</td>
<td>NCT0120081 (8/2011)</td>
<td>Not yet reported</td>
<td>Recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td>NVP-BKM120</td>
<td>Pan-PI3K</td>
<td>Adjunct only</td>
<td>NCT01397877 (7/2011)</td>
<td>Not yet reported</td>
<td>Recruiting, not reported</td>
<td></td>
</tr>
<tr>
<td>NVP-BKM120</td>
<td>Pan-PI3K</td>
<td>Adjunct only</td>
<td>NCT0159380 (8/2011)</td>
<td>Not yet reported</td>
<td>Recruiting, not reported</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: NCT #, National Clinical Trial identifier; temsirolimus was previously known as CCI-772; everolimus was previously known as RAD001; ridaforolimus has been previously known as deforolimus, AP23573, and MK-8669; SAR245408 was previously known as XL147; PF-05212384 was previously known as PKI-587; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; Grade 3 AE, adverse events as per Common Terminology Criteria for Adverse Events.

Objective response by independent review.

*Duration of SD was presumed to be first planned radiographic evaluation of disease if not specifically reported.

**Eligibility was restricted to endometroid histology.

†This was a study of AP23573, an IV formulation of ridaforolimus.
<table>
<thead>
<tr>
<th>Investigational/therapeutic agents</th>
<th>Targets</th>
<th>Treatment population</th>
<th>NCT # (date registered)</th>
<th>Clinical results</th>
<th>Toxicities</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus and carboplatin/paclitaxel</td>
<td>mTORC and cytotoxic</td>
<td>Chemo-naive</td>
<td>NCT00977574 (9/2009)</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Temsirolimus and bevacizumab</td>
<td>mTOR and VEGFA</td>
<td>1–2 prior lines</td>
<td>NCT00723255 (7/2008)</td>
<td>CR (1/53) PR (11/53) SD ≥ 8 weeks (27/53) PFS ≥ 6 months (23/53)</td>
<td>Most common ≥ grade 3 AEs: Neutropenia, cardiac, constitutional, gastrointestinal, infection, metabolic, pain. (3 deaths possibly attributed to drug)</td>
<td>49</td>
</tr>
<tr>
<td>Temsirolimus vs. temsirolimus/megace/tamoxifen</td>
<td>mTOR and hormonal therapy</td>
<td>Adjuvant only</td>
<td>NCT00729586 (8/2008)</td>
<td>Combo arm: CR (0/22) PR (3/22) SD ≥ 8 weeks (11/22) Single arm: CR (2/20) PR (4/20) SD ≥ 8 weeks (11/22)</td>
<td>Combo arm: most common ≥ grade 3 AE: Vascular, edema, fatigue. (7 thromboembolic events, 1 sudden death, 1 myocardial infarction) Single arm: most common ≥ grade 3 AE: anemia, nausea, hyperglycemia</td>
<td>48</td>
</tr>
<tr>
<td>Everolimus and letrozole</td>
<td>mTOR and hormonal therapy</td>
<td>1–2 lines</td>
<td>NCT01068249 (2/2010)</td>
<td>CR (5/42) PR (2/42) SD ≥ 8 weeks (10/42)</td>
<td>The most common drug related toxicities were fatigue, diarrhea, thrombocytopenia</td>
<td>47</td>
</tr>
<tr>
<td>Everolimus and letrozole and metformin</td>
<td>mTOR and hormonal therapy and cellular nutrient withdrawal</td>
<td>1–2 lines</td>
<td>NCT01797523 (2/2013)</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
<td></td>
</tr>
</tbody>
</table>

NCT #, National Clinical Trial Identifier; temsirolimus was previously known as CCI-779; everolimus was previously known as RAD001; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; AE, adverse events; Grade 3, as per Common Terminology Criteria for Adverse Events.

aStudies were identified through www.clinicaltrials.gov and data collected through www.clinicaltrials.gov and Trialtrove (www.citeline.com/products/trialtrove). Phase II studies with a primary focus of endometrial cancer are included. Phase IB expansion and phase II studies with multiple cancers of origin are not included. All numbers in the denominator are enrolled patients on the study.

bDuration of SD was presumed to be first planned radiographic evaluation of disease if not specifically reported.

cThis described target recognizes the incomplete understanding of metformin as a potential anticancer therapy.
The rapalogs continue to be studied in combination with other cytotoxic and biologic agents. Phase II studies of rapalogs with hormonal agents as well as antiangiogenic agents have been completed (refs. 47–49; Table 2). Toxicity of these combinations may be limiting. The combination arm of GOG 248, a randomized study of temsirolimus with or without hormonal therapy was terminated because of thromboembolic events (48). Combinations of rapalogs and antiangiogenic agents also report high rates of vascular events (49; Susan Campos; personal communication).

GOG 86P is a “pick-the-winner” randomized phase II study evaluating 3 different agents, including temsirolimus, in combination with carboplatin and paclitaxel. This study has embedded translational studies that could be informative. Should a predictive biomarker for single-agent rapalog response be identified, it will be important to know whether it can be generalized to rapalogs in therapeutic combinations.

PI3K pathway inhibitors

Rapalogs are incomplete inhibitors of mTORC1 targets and, due to feedback loops, can result in activation of upstream PI3K signals (50, 51). It has been hypothesized that newer PI3K pathway agents, which target further upstream in the pathway, will be more clinically effective. Numerous phase Ib/II clinical trials are underway including pan-PI3K, dual PI3K/mTOR, AKT, and catalytic mTOR inhibitors (www.clinicaltrials.gov; Table 1). Although clinical reports are expected soon, the results for the majority of these studies have yet to be reported. Results from a phase II study of MK-2206, an allosteric AKT inhibitor were recently reported (52). This study was prospectively stratified for PIK3CA mutations and was designed to explore the hypothesis that patients with tumors that harbor PIK3CA mutation would be more likely to derive benefit from MK-2206. Of the 36 patients enrolled, 9 were classified as PIK3CA mutant and 27 were PIK3CA wild-type. There was 1 event of clinical benefit in the PIK3CA-mutant group and 4 events of clinical benefit in the PIK3CA wild-type group suggesting that there is limited clinical use for prospective PIK3CA mutation testing predict response to AKT inhibitors. All 4 participants who were on treatment for more than 6 months had tumors of serous histology, a histology that represents a disproportionate number of deaths from endometrial cancer.

PI3K pathway inhibitors are also being evaluated in combination studies. On the basis of the tight networking with the RAS-ERK pathway combination of MEK and other RTK inhibitors are of great interest. Phase I studies of combination have identified notable responses in endometrial cancer though exploration of dosing to minimizing toxicity continues (53). PI3K pathway inhibitors are also being studied in combination with cytotoxics (Table 2 and www.clinicaltrials.gov) though efficacy results in endometrial cancer have yet to be reported.

The future: contextualizing PI3K signaling

Results from many PI3K pathway inhibitors trials are anticipated. (Tables 1 and 2). However, these first reports suggest that PI3K/mTOR pathway inhibitors as single agents are not as efficacious as hoped. In recognition that clinical trials should generate as well as test hypotheses, there are some avenues that warrant further exploration.

Of drugs and targets. Preclinical and translational data strongly support that PI3K signaling underpins endometrial cancer biology and this prior knowledge needs to be accounted for in the interpretation of PI3K/mTOR pathway inhibitor trial results. At this early juncture, negative studies in this disease should steer focus to the investigational agents as much as challenge the validity of PI3K as a target. Pharmacodynamic studies to verify pathway inhibition at achievable exposures should remain an integral part of these early-phase studies as the maximal tolerated may not equate to the biologically optimal dose. The enhanced specificity and potency of newer classes of agents such as the mTORC1/2 catalytic and PI3K isomform-specific inhibitors hold promise and should also be evaluated in endometrial cancer.

Metabolic context. Obesity is an established risk factor for developing endometrial cancer with a nearly 3-fold increase in risk (4). The biology underlying the associations between obesity, endometrial cancer risk, and outcomes remains incompletely understood. However, chronic overexposure to hormones elevated in the obese state such as insulin, insulin-like growth factors, and estrogens, likely contribute (54). The PI3K pathway is the key-regulating pathway of glucose uptake and metabolism (6) perhaps suggesting that PI3K pathway alteration may need to be explored in the context of a patient’s metabolic state. Recent studies evaluating the association of PI3K pathway alterations show an interaction between PTEN protein loss, obesity, and prognosis. Patients with obesity with PTEN loss have improved outcomes as compared with those with PTEN retained. In contrast, in the nonobese population, patients with PTEN loss have worse outcomes (55). In addition, retrospective analysis of the combination study of everolimus and letrozole show a clinical benefit rate that is twice as high in patients taking the antidiabetic agent metformin as compared with those who are not (56). Whether metformin is merely associated with a subpopulation of patients whose endometrial cancer is more like to response to rapalogs or whether there is a causal effect (direct or indirect) remains unclear.

Histologic context. Unlike breast cancers, treatment recommendations for endometrial cancers are not based...
on upfront molecular classifications. The most common endometrial cancer histologies (endometroid, papillary serous, clear cell, mixed) are treated with the same chemotherapy regimens. Results from the MK-2206 trial, in which all patients with 6 months of progression-free survival had tumors of serous histology suggest that a more nuanced approach may be warranted. Isolated molecular differences between these histologies have been described (27). Recent studies of whole-exome sequencing of uterine papillary serous cancers further detail the differences and have identified candidate molecular changes to explore as potential molecular biomarkers for AKT inhibitor response (57–59). In addition, these studies may be useful for the classification of endometrial cancers that are challenging to classify by histology alone (60).

**Mutational context.** Comprehensive genome studies including the The Cancer Genome Atlas highlights some interesting features of the PI3K pathway that seem to be particular to endometrial cancer (17, 28). Unlike other cancers, comutations within the PI3K pathway are common. There is a strong association of PIK3CA and PTEN as well as PIK3R1 and PTEN mutations. PIK3R1 and PIK3CA comutation are uncommon and PTEN as well as PIK3CA are common. There is a strong association of other cancers, comutations within the PI3K pathway to be particular to endometrial cancer (17, 28). Unlike some interesting features of the PI3K pathway that seem to be particular to endometrial cancer (17, 28), PIK3CA mutations are distributed differently in endometrial cancers than other cancers in which PIK3CA mutations are common such as breast cancer (26). Functional studies suggest that not all mutations in PIK3CA and PIK3R1 have the same cellular impact (28). How these very specific mutational features impact endometrial cancer biology and clinical outcomes are under investigation.

In conclusion, the PI3K pathway underlies endometrial cancer development and remains a key target for new therapeutics. Ongoing and future clinical investigation should recognize the intricacies of this pathway as highlighted above. Translational studies should be comprehensive including complete sequencing and copy number analysis and pharmacodynamic studies; tumors from patients with robust responses should be studied in detail metabolic data such as body mass index, presence of diabetes, and use of antidiabetic agents should be collected. Together with emerging clinical reports these data can help guide the optimal development of PI3K pathway inhibitors in endometrial cancer.

**Disclosure of Potential Conflicts of Interest**

A.P. Myers is employed as a clinical program leader for Novartis and is a consultant/advisory board member of Eisai and Sanofi.

**Acknowledgments**

The authors thank C. Dibble and B. Emerling for thoughtful input and L. Cantley, G. Mills, and U. Matulonis for mentorship. The author would like to apologize in advance to investigators whose work could not be primarily cited due to space limitations.

**Grant Support**

This work was supported by a Stand Up To Cancer Dream Team Translational Cancer Research Grant, a Program of the Entertainment Industry Foundation (SU2C-AACR-DT 0209).

Received April 29, 2013; revised July 17, 2013; accepted July 28, 2013; published online October 2, 2013.

**References**

Targeting the PI3K/mTOR Pathway in Endometrial Cancer


New Strategies in Endometrial Cancer: Targeting the PI3K/mTOR Pathway—The Devil Is in the Details

Andrea P. Myers


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/19/19/5264

Cited articles
This article cites 49 articles, 24 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/19/19/5264.full#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/19/19/5264.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the ACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the ACR Publications Department at permissions@aacr.org.