Title
Targeting fibroblast growth factor pathways in endometrial cancer

Journal
Current Problems in Cancer, 41(1)

ISSN
0147-0272

Authors
Winterhoff, Boris
Konecny, Gottfried E

Publication Date
2017

DOI
10.1016/j.currproblcancer.2016.11.002

Peer reviewed

Curr Probl Cancer 41 (2017) 37–47

Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Targeting fibroblast growth factor pathways in endometrial cancer

Boris Winterhoff, MD[a], Gottfried E. Konecny, MD[b,*]

ARTICLE INFO

Keywords:
Endometrial cancer
Fibroblast growth factor
Angiogenesis

ABSTRACT

Novel treatments that improve outcomes for patients with recurrent or metastatic endometrial cancer (EC) remain an unmet need. Aberrant signaling by fibroblast growth factors (FGFs) and FGF receptors (FGFRs) has been implicated in several human cancers. Activating mutations in *FGFR2* have been found in up to 16% of ECs, suggesting an opportunity for targeted therapy. This review summarizes the role of the FGF pathway in angiogenesis and EC, and provides an overview of FGFR-targeted therapies under clinical development for the treatment of EC.

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer, with 54,870 new cases and 10,170 related deaths estimated for the United States in 2015.[1] Localized disease is often curable with surgery and the 5-year relative survival rate for patients diagnosed with early-stage EC is high.[1-3] However, for patients who present with metastatic disease or experience a recurrence, prognosis is poor.[1-3] Response of metastatic EC to standard therapies (eg, adjuvant radiotherapy, brachytherapy, or chemotherapy) is limited and overall survival for most patients with recurrent or metastatic disease is ≤ 1 year.[2-4] Thus, novel treatment options for this disease remain an unmet need.

[a] *Department of Obstetrics and Gynecology, University of Minnesota, Minneapolis, Minnesota*
[b] *Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California*
**Correspondence to: Gottfried E. Konecny, Department of Medicine David Geffen School of Medicine University of California, Los Angeles 100 Medical Plaza, Suite 550, Los Angeles, CA 90025.*
E-mail address: gkonecny@mednet.ucla.edu (G.E. Konecny).

http://dx.doi.org/10.1016/j.currproblcancer.2016.11.002

EC is classified predominately into 2 types and they are type I endometrioid and type II nonendometrioid.[3] Type I EC is associated with atypical hyperplasia as a precursor, and generally develops at an earlier age at a low stage and grade. In contrast, type II EC involves atrophic endometrium, proceeds through a precursor known as endometrial intraepithelial carcinoma, and presents in older patients and at a higher stage and grade. Type I EC is associated with endometrioid histopathology, whereas type II is linked to the serous subtype.

A range of genetic abnormalities are found in EC. Microsatellite instability (MSI) is present in 25%-30% of endometrial tumors and is most common in type I EC.[5,6] PTEN alterations are also found in 37%-61% of type I EC and lead to deregulation of the PI3K/AKT pathway.[7] Other common mutations include those in *PIK3CA* and *K-RAS*.[7,8] *FGFR2* mutations are associated with EC and are found in approximately 10%-16% of cases.[8-12] Type II tumors generally display *p53* mutations, are estrogen receptor or progesterone receptor negative, do not show MSI, and generally do not demonstrate *FGFR2* mutations.[9,11-16]

FGF or FGFR biology and FGFR signaling

The fibroblast growth factor (FGF) family consists of 4 fibroblast growth factor receptor (FGFR) tyrosine kinases, designated FGFR1-4, and 22 FGF ligands.[17] Each FGFR possesses an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain.[17] When FGFRs bind to the small polypeptide FGF ligands that primarily reside in the extracellular matrix, they dimerize and activate their kinase domains via transautophosphorylation.[17,18] Members of the FGFR receptor tyrosine kinase family are differentially activated by binding to a subset of FGFs in conjunction with heparan sulfate proteoglycan, which stabilizes and sequesters FGFs.[19]

Ligand specificity of FGFR1-3 is, in part, controlled by an alternative splicing event that affects the third immunoglobulin loop (IgIII) in the ligand-binding domain, resulting in an IIIb isoform preferentially expressed in epithelial cells and an IIIc isoform preferentially expressed in mesenchymal cells. FGF3, FGF7, FGF10, and FGF22 exclusively bind the IIIb isoform, FGF1 binds both the IIIb and IIIc isoforms, and the remaining FGF ligands preferentially bind the IIIc isoform.[20] Importantly, ligand expression is controlled cell-specifically, such that physiological receptor stimulation tends to occur in a paracrine rather than an autocrine manner.[21]

On ligand binding and receptor dimerization, the tyrosine kinase domains undergo phosphorylation. Phosphotyrosine residues are then able to act as docking sites for intracellular proteins, leading to activation of signaling cascades (Fig).[22,23] A total of 4 main signaling pathways can be activated such as MAPK, PI3K/AKT, PLCγ, and STAT.[22] Activation of the MAPK pathway leads to translocation of cell cycle–activating transcription factors to the nucleus (eg, MYC), whereas PI3K/AKT signaling results in initiation of antiapoptotic pathways, as well as cell growth and proliferation. Enhanced MAPK signaling occurs via PLCγ activation. Furthermore, STAT-dimers translocate to the nucleus to activate or repress gene transcription.[21] Regulation of FGF signaling is important to ensure a balanced response to receptor stimulation. This occurs largely through negative feedback mechanisms, including receptor internalization via ubiquitination and induction of negative regulators (eg, SPRY, SPRED1 and 2, and SEF).[24-27]

Impaired FGF pathway signaling can lead to increased cell survival, increased cell motility, and tumor angiogenesis, and has been implicated in many types of cancer, including EC.[9,18] *FGFR2* activation has been associated with tumorigenesis, whereas FGFR1 expression has been associated with tumor progression.[8,28] Among the many FGF ligands, FGF1 and FGF2 appear to play the largest roles in cancer. Both of these ligands act as tumor growth factors that can increase the motility and invasiveness of cancers.[28,29]

FGFR and angiogenesis

In normal settings, FGF or FGFR signaling was first shown to have a key role in promoting embryogenesis, angiogenesis, and wound healing. As drivers of angiogenic signaling, FGF1 and FGF2 are known to directly mediate proliferation, migration, vessel formation, and maturation of

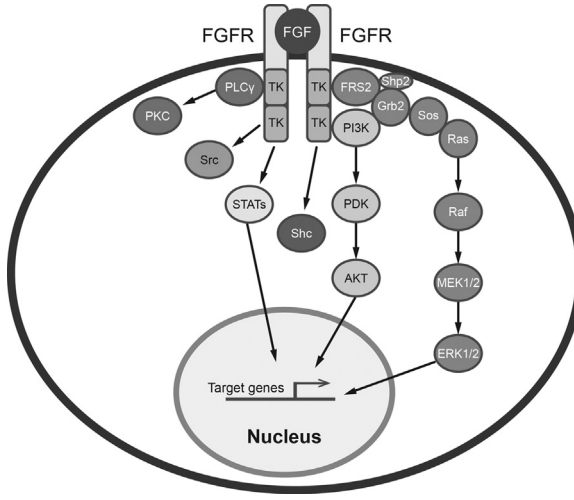

Fig. FGF signaling pathways. FGF ligands bind to FGFRs, resulting in dimerization of the FGFRs, activation of FGFR kinase domains via transautophosphorylation, and signal transduction through multiple pathways.

endothelial cells.[21,30] Additionally, FGFs have demonstrated indirect synergism with vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) pathways in preclinical models, where addition of both FGF2 and VEGF resulted in a more rapid angiogenic response than the addition of either of the factor alone.[31]

FGFs may also play a role in cancer progression by promoting endothelial cell tumor angiogenesis through both paracrine and autocrine (ie, release of FGFs from capillary endothelial cells) mechanisms.[21,32] In preclinical solid tumor models, delivery of antisense FGF2 complementary DNA was shown to inhibit angiogenesis and exhibit antitumor activity.[33] Additionally, FGF1 overexpression was recently shown to correlate with microvessel tumor density and poor survival in patients with ovarian cancer.[34] Simultaneous VEGF and FGF2 expression in xenograft models was shown to enhance tumor growth, blood vessel density, and permeability, suggesting that synergy between FGFs and other angiogenesis pathways may exist in the disease setting as well. Reducing FGF2 expression in this preclinical model resulted in significantly decreased tumor volume and vessel density, whereas inhibiting VEGF disrupted pericyte organization and permeability.[21,35]

The integrated mechanisms of FGFR and VEGF receptor (VEGFR) pathways in tumor angiogenesis via partially overlapping functions suggest that FGF or FGFR upregulation may also play a role in anti-VEGF therapy resistance.[21] Preclinical tumor models that progressed after an initial response to anti-VEGF agents were shown to exhibit increased FGF2 expression at time of progression than tumors that did not progress.[36] Similar changes in FGF2 expression were observed for patients with colorectal cancer that progressed after bevacizumab-based treatments and in patients with glioblastoma that progressed after VEGFR tyrosine kinase inhibitor therapy.[30]

Angiogenic targets in EC

Angiogenesis plays an important role in EC, with angiogenic growth factors found to be highly expressed in endometrial tumors, suggesting an opportunity for antiangiogenic targeted therapy in this disease.[37–39] The VEGF family of proteins binds to and activates cell-surface VEGF tyrosine kinase receptors (VEGFR1-3).[40] High levels of VEGF expression have been found in endometrial tumors and associated with advanced stage, high tumor grade, deep myometrial invasion, lymphovascular invasion, lymph node metastases, and poor clinical outcome.[41] Given these results, clinical trials in EC were conducted with several agents that target the VEGF

pathway, including tyrosine kinase inhibitors (sunitinib and sorafenib), an immunomodulatory drug (thalidomide), a monoclonal antibody (bevacizumab), and a VEGF-trap (aflibercept; Table 1). Most of these agents, however, only showed modest activity, with response rates ranging from 4%-18% and median overall survival of 5.9-19.4 months. Additional antiangiogenic agents in development, including pazopanib, cediranib, and trebananib, have demonstrated improved progression-free or overall survival or both in other gynecologic cancers (eg, ovarian and cervical), but these benefits have yet to be shown in patients with EC.[42]

Unsurprisingly, cancers develop resistance to VEGF pathway inhibitors. A mechanism by which this may happen is a process known as angiogenic escape, in which alternative angiogenic pathways are used by the tumors.[36] The FGF pathway also plays an important role in angiogenesis in addition to its role in tumor development, growth, and progression.[28,43] Resistance to VEGF inhibitors can be overcome by inhibiting the FGF pathway.[36] Therefore, there has been recent interest in targeting the FGF pathway, alone or in combination with VEGF pathway inhibition, in the treatment of many types of cancer, including EC.

Potential of targeting the FGF pathway in EC

FGFR2 mutations have been found in up to 16% of endometrial tumors, primarily those of endometrioid histology, using traditional and high-throughput sequencing methods.[8,9,11,12,44-48] Endometrial tumor-associated *FGFR2* mutations result in the expression of mutated receptors that are constitutively activated and usually oncogenic (Table 2).[11,12,18] These mutations also increase ligand binding affinity and decrease specificity.[49-51] Most commonly found in endometrial tumors with MSI, *FGFR2* mutations have been associated with shorter disease-free ($P = 0.008$) and overall survival ($P = 0.025$) in patients with early-stage EC.[44,45] Thus, *FGFR2* mutational status could potentially be used to identify patients who may benefit from more aggressive adjuvant radiation or chemotherapy after surgery.

Table 1
Clinical data for VEGF pathway-targeted therapies in endometrial cancer.

Agent	Target(s)	Phase	Patients, *n*	Population	Efficacy data
Sunitinib	VEGFR1-3, PDGFRα and PDGFRβ, c-Kit, RET, CSF-1R, flt3	2	33	Recurrent or metastatic EC	ORR, 18.1%; PR, 18.1%; PFS, 3 mo; OS, 19.4 mo[72]
Sorafenib	Raf kinase, VEGFR2/3, PDGFRβ, flt3, c-Kit, and RET	2	56	Advanced or recurrent uterine carcinoma	ORR, 5%; PR, 5%; 6-mo PFS, 29%; OS, 11.4 mo[73]
Thalidomide	VEGF, FGF2	2	24	Persistent or recurrent chemotherapy-refractory EC	ORR, 12.5%; PR, 12.5%; PFS, 1.7 mo; OS, 6.3 mo[74]
		2	45	Uterine carcinoma	ORR, 4%; PR, 4%; PFS, 1.9 mo; OS, 5.9 mo[75]
Bevacizumab	VEGF-A	2	52	Persistent or recurrent EC	ORR, 13.5%; CR, 1.9%; PR, 11.5%; PFS, 4.2 mo; OS, 10.5 mo[76]
Bevacizumab + temsirolimus	VEGF-A; mTOR/ hypoxia-inducible factor	2	49	Persistent or recurrent EC	ORR, 24.5%; CR, 2%; PR, 22.4%; PFS, 5.6 mo; OS, 16.9 mo[77]
Aflibercept	VEGF-A/B, PlGF	2	44	Persistent or recurrent EC	ORR, 7%; PR, 7%; PDS, 2.9 mo; OS, 14.6 mo[78]

CR, complete response; CSF-1R, colony stimulating factor 1 receptor; EC, endometrial cancer; mo, months; mTOR, mammalian target of rapamycin; flt3, Fms-like tyrosine kinase 3; ORR, overall response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PlGF, placental growth factor; PR, partial response.

Table 2
FGFR2 mutations in endometrial cancer.

FGFR2 mutation	Oncogenic[a]	Drug sensitivity[a]
D101Y[11]	Yes	Not tested
S252W[11,12,53]	Yes	Yes
P253R[11,79]	Yes	Not tested
K310R[11,12]	No	NA
A314D[11]	Not tested	Not tested
A315T[12]	Not tested	Not tested
S373C[12]	Not tested	Not tested
Y376C[12]	Not tested	Not tested
C382R[12,80]	Yes	Not tested
A389T[11]	No	NA
N549K[11]	Yes	Yes
N550K[11,12,53]	Yes	Yes
K660E[11]	Not tested	Not tested
K659N[11]	Not tested	Not tested
L764fs*4[18,81]	Yes	Not tested

[a] Defined by cellular assays or animal models.

Overexpression of the FGFR2 isoform IIIc (FGFR2 IIIc) has been observed in endometrial endometrioid carcinomas relative to normal endometrium tissue ($P < 0.05$), suggesting a role for FGFR2 IIIc expression in endometrial tumorigenesis; however, lack of association with lymph node metastases and tumor stage indicates that FGFR 2IIIc is not related to disease progression.[52]

Preclinical studies have shown that inhibition of FGFR2 in EC cell lines with *FGFR2* mutations inhibits proliferation and induces cell death, even within the context of concomitant mutations, suggesting that FGFR2 may be a viable therapeutic target in EC.[8,11,53] *FGFR2* mutations resulting in increased kinase activity (eg, N550K) have also been shown to contribute to endometrial cell line resistance to FGFR inhibitors, indicating that small molecules targeting active FGFR confirmations should be used to treat EC with activating *FGFR2* mutations.[54]

Integrated genomic characterization of somatic copy number alterations demonstrated that *FGFR1* and *FGFR3* amplifications can also occur in EC. Furthermore, in this analysis, *FGFR1* and *FGFR3* amplifications were associated with hierarchically clustered tumors with significantly worse progression-free survival than tumors in other endometrioid cluster groups.[16]

In addition to FGFR aberrations, studies have also shown that FGF expression is altered in EC. FGF2 expression is significantly higher in hyperplastic and malignant endometrial tissue when compared with normal endometrial tissue, and expression increases as the disease progresses.[55-58] Likewise, FGF1 expression increases with grade, myometrial invasion, and staging.[58] In preclinical studies, FP-1039, a soluble fusion protein inhibitor of FGF1, FGF2, and FGF4, showed antiproliferative activity in endometrial carcinoma cell lines and mouse xenografts.[59,60] Thus, agents that target FGF signaling or multiple kinases involved in angiogenesis and tumorigenesis may be particularly effective.

FGFR2 mutations in EC have been identified in a number of independent studies.[11,12,44] Interestingly, most somatic *FGFR2* mutations in EC are identical to germline mutations in developmental disorders (eg, craniosynostosis syndromes).[12] The S252W mutation, the most common *FGFR2* mutation in EC, occurs in the linker region between the IgII and IgIII loops, the area responsible for providing key contacts with the ligand. This mutation increases the binding affinity of the receptor for a range of FGFs while also leading to violation of ligand specificity of the receptor isoforms.[18] It is also possible that this mutation leads to the modified receptor remaining on the cell surface for an extended period of time, rather than undergoing rapid recycling like its wild type counterpart.[61] Mutations in the kinase domain, such as N550K, lead

to constitutive activation of the receptor, whereas others, including S373C and Y376C, result in gain of a cysteine residue, allowing formation of intermolecular disulfide bonds.[62] All of these mutations then affect downstream signaling mechanisms, leading to increased cell proliferation and migration, and premature differentiation. Initial studies have shown inhibition of FGFR2 using PD173074 or TKI258, as well as receptor knockdown, in EC cells leads to a reduction in cell survival.[8,11,53]

In EC, mutations in *FGFR2* are mutually exclusive with those in *KRAS*; however, 77% of endometrial tumors with mutations in *FGFR2* also harbor PTEN mutations.[8] It is, therefore, possible that the aberrant signaling of the mTOR pathway, in conjunction with the FGFR2 pathway, drives tumorigenesis in this subset of endometrial tumors. This has been demonstrated recently, where treatment of EC cells with ponatinib, an FGFR inhibitor, and ridaforolimus, an mTOR inhibitor, resulted in a combined antiproliferative effect.[63] Strong synergy between the 2 drugs was shown, defined by CI $<$ 0.1, resulting in G1 arrest of EC cells. The ability of FGFR inhibition to synergize with chemotherapeutic drugs has also been shown in EC.[44] Both of these studies support the prospect of dual drug therapy in treatment of this cancer.[63]

FGFR-targeted therapies in EC

Several FGFR-targeted therapies, including brivanib, nintedanib, dovitinib, lenvatinib and ponatinib, have shown preclinical activity and have been investigated in clinical trials in patients with EC (Table 3).

Brivanib

Brivanib is a tyrosine kinase inhibitor that targets VEGFR2/3 and FGFR1/2. A phase 2 study investigated brivanib in 43 evaluable patients with recurrent or persistent EC who had been treated with 1 or 2 previous cytotoxic regimens (NCT00888173). Patients received 800 mg of

Table 3
Clinical data for FGFR-targeted therapies in endometrial cancer.

Agent	Target(s)	Phase	Patients, *n*	Population	Efficacy data	NCT ID
Brivanib	VEGFR2/3, FGFR1/2	2	43	Recurrent or persistent EC	ORR, 18.6%; CR, 2.3%; PR, 16.3%; PFS, 3.3 mo; OS, 10.7 mo[64]	NCT00888173
Nintedanib	PDGFRα/β, FGFR1–3, VEGF-R1-3	2	32	Recurrent or persistent EC	ORR, 9.4%; PR, 9.4%; PFS, 3.3 mo; OS, 10.1 mo[65]	NCT01225887
Dovitinib	FGFR1-3, VEGF-R1-3, PDGFR	2	22 *FGFR2*-mutated, 31 *FGFR2*-nonmutated	Advanced or metastatic EC or both	*FGFR2*-mutated: ORR, 5%; PR, 5%; PFS, 4.1 mo; OS, 20.2 mo; *FGFR2*-nonmutated: ORR,16%; PR, 16%; PFS, 2.7 mo; OS, 9.3 mo[66]	NCT01379534
Lenvatinib	VEGFR1-3, FGFR1-4, PDGFRα, RET, c-Kit	2	133	Advanced EC and PD after Pt-based chemotherapy	ORR, 14.3%-21.8%; PFS, 5.4 mo; OS, 10.6 mo[69]	NCT01111461

CR, complete response; EC, endometrial cancer; FGFR, fibroblast growth factor receptor; ORR, overall response rate; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PR, partial response.

brivanib orally daily. In total, 19% of patients responded (2% achieved a complete response and 16% a partial response). Median progression-free survival was 3.3 months and median overall survival was 10.7 months. The investigators found that VEGF and angiopoietin-2 expression in combination predicted progression-free survival, and estrogen receptor-α positively correlated with overall survival. Only 3 patients had tumors with *FGFR2* mutations, limiting a robust analysis of the effect of FGFR pathway inhibition on *FGFR2*-mutated tumors. Brivanib was reasonably well tolerated. The most common grade 3/4 adverse events (AEs) were cardiac (21%), gastrointestinal (16%), metabolic (14%), and nausea (12%). Notable side effects included 1 rectal fistula, 9 cases of grade 3 hypertension, and 1 case of grade 4 confusion. In addition, 1 patient died of multiorgan failure.[64]

Nintedanib

Nintedanib inhibits PDGFRα/β, FGFR1-3, and VEGFR1-3. In a phase 2 study of 32 patients with recurrent or persistent EC (NCT01225887), nintedanib had an overall response rate of 9% (all partial responses). Median progression-free survival was 3.3 months, and median overall survival was 10.1 months. The most common grade 3 AEs were gastrointestinal toxicity (16%) and liver function abnormalities (16%); however, there were no grade 4 AEs. Tumor and blood samples were not collected, preventing correlative analyses for biomarkers and *FGFR* mutation status.[65]

Dovitinib

Dovitinib can inhibit tumor growth and angiogenesis through FGFR1-3, VEGFR1-3, and PDGFR. In preclinical studies, dovitinib significantly inhibited the growth of *FGFR2*-mutated and -nonmutated endometrial xenografts.[53] A phase 2 study investigated dovitinib as second-line therapy in patients with advanced or metastatic EC or both; however, 22 patients had *FGFR2*-mutated tumors and 31 had *FGFR2*-nonmutated tumors (NCT01379534). This was the largest trial of an FGFR inhibitor in this patient population and the first to prospectively screen patients for *FGFR2* mutational status.[66,67]

Initial results showed that 5% of patients with *FGFR2* mutations achieved a partial response and 59% achieved stable disease, and 16% of patients with *FGFR2*-nonmutated cancer achieved a partial response and 35% achieved stable disease. Median progression–free survival (95% CI) was 4.1 months (2.6-5.5) for patients with *FGFR2*-mutated cancer and 2.7 months (1.4-6.8) for those without the mutation. Median overall survival (95% CI) was 20.2 months (8.2-20.2) and 9.3 months (6.0-15.2), respectively. The most common AEs were gastrointestinal and were similar between the 2 groups. The most common grade 3/4 AEs were hypertension (17%), diarrhea (9%), fatigue (8%), and rash (8%). The most common AEs leading to discontinuation were deep vein thrombosis, pulmonary embolism, and small intestinal obstruction (3.8% each).[66,67]

Lenvatinib

Lenvatinib is a multikinase inhibitor that targets VEGFR1-3, FGFR1-4, PDGFR, RET, and c-Kit. In a phase 1, dose-escalation trial of lenvatinib in patients with advanced solid tumors, response was achieved by 1 of 4 patients with EC enrolled on the study.[68] A phase 2 study is investigating lenvatinib in patients with advanced EC and disease progression after platinum-based chemotherapy (NCT01111461). Patients received 24 mg of lenvatinib daily until disease progression or toxicities became unmanageable. Initial results showed that among 133 patients, 14% of patients responded according to independent review and 22% by investigator assessment. Median progression-free survival was 5.4 months, and median overall survival was 10.6 months. The most common grade 3/4 AEs were hypertension (33%), fatigue (12.8%), and diarrhea (5.3%). Of note, 1 patient had grade 5 asthenia.[69]

Baseline plasma angiopoietin-2 levels correlated with tumor shrinkage, objective response rate, progression-free survival, and overall survival. Patients with low baseline levels (<2082 pg/mL) had improved ORR (61% vs 18%), median progression-free survival (9.5 vs 3.7 months), and median overall survival (23.0 vs 8.9 months). Additional cytokine and angiogenic factors (interleukin-8, hepatocyte growth factor, VEGFA, placental growth factor, Tie-2, and tumor necrosis factor α) also correlated with survival. Patients with a *PIK3CA* mutation showed a trend toward shorter overall survival ($P = 0.085$). Gene expression profiling demonstrated that MAPK and PI3K signaling pathways contributed to lenvatinib resistance.[70]

Ponatinib

Ponatinib is a pan-FGFR inhibitor that targets the FGFR family of kinases (FGFR1-4). In vitro, ponatinib inhibited FGFR signaling and cell growth of *FGFR2*-mutant EC cells. In addition, ponatinib has been shown to reduce tumor growth by 82% in an endometrial tumor model in mice.[71] These data supported the design of a pilot study to evaluate the effectiveness of ponatinib in *FGFR2*-mutated recurrent or persistent EC (NCT01888562); however, this study was withdrawn before recruitment started. A preclinical study also showed that ponatinib in combination with ridaforolimus, an mTOR inhibitor, synergistically inhibited growth of *FGFR2*-mutant EC cells and tumor growth in an endometrial xenograft model.[63] Currently, there are no ongoing studies investigating ponatinib in EC.

Next steps

Current evidence suggests that the FGF pathway is a viable therapeutic target for EC. Although only indirect comparisons can be made, study results suggest that FGFR and VEGF pathway inhibitors may have similar activity, providing an additional treatment option for patients with recurrent or persistent EC. As agents inhibiting the FGF pathway undergo further development for the treatment of EC, several challenges remain, including patient selection, trial recruitment, choice of drug family (ie, selective vs nonselective inhibitors), and disease setting.[21]

Results from preclinical studies suggest that patient selection may further improve the activity of FGFR inhibitors; however, conclusions from currently available clinical data (eg, dovitinib) are unclear.[21,66] Although a pilot study of ponatinib would also be evaluating efficacy and safety specifically in patients with *FGFR2*-mutant EC, additional trials are needed to determine whether patient selection improves the efficacy of FGF pathway-targeting agents in this disease. Validation of the activity of anti-FGFR agents in EC would likely need to occur in randomized trials of patients with specific *FGFR* aberrations.[21] Because, as described earlier, FGFR aberrations occur in $<20\%$ of EC cases, development of robust molecular screening tools will be crucial for successful recruitment of these patients onto such trials.

To further elucidate appropriate patient selection strategies, research is also needed to determine whether specific biomarkers can be used to predict patients most likely to respond to selective FGFR inhibitors or tyrosine kinase inhibitors. For example, results from the phase 2 brivanib study showed that VEGF and angiopoietin-2 expression predicted progression-free survival and estrogen receptor-α correlated with overall survival.[64] Similarly, results from the phase 2 lenvatinib study showed that baseline angiopoietin-2 levels correlated with outcomes.[69]

All current FGFR inhibitors with clinical data in the advanced EC setting also inhibit additional targets that may play a role in disease progression. It is not fully known whether the activity of these agents is owing to their inhibition of FGFR, one of their other targets or a combination, making it challenging to understand the true value of FGFR inhibition. Studies of agents more selective for FGFRs (eg, ponatinib) may help to clarify the specific role of FGFR inhibition in the treatment of EC. FGFR inhibitors with activity against other angiogenesis targets may also have potential in maintenance therapy, where the use of these agents after chemotherapy may delay progression and enhance progression-free survival; however, investigation in this setting is also needed.

Conclusions

There is a strong need for novel treatments that extend progression-free survival and overall survival for patients with recurrent or metastatic EC. The FGF pathway plays an important role in tumor angiogenesis and angiogenic escape during inhibition of the VEGF pathway. Clinical results show that FGFR inhibitors brivanib, dovitinib, and lenvatinib are active in EC. More studies are needed to determine whether biomarker screening may be an effective option for personalizing care with FGFR inhibitors.

Acknowledgments

The authors thank Pamela Pollock for providing comments that greatly improved the article. Medical editorial assistance was provided by Amanda L. Kauffman, PhD; Julie Shilane, PhD; and Peter J. Simon, PhD; and financially supported by Novartis Pharmaceuticals Corporation.

References

1. National Cancer Institute. Cancer of the endometrium. SEER Stat Fact Sheets; 2015.
2. National Comprehensive Cancer Network. Uterine neoplasms, version 2.2015. http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf; 2015.
3. Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, Mariani A, Dowdy SC. Current issues in the management of endometrial cancer. *Mayo Clin Proc* 2008;83(1):97–112.
4. Carlson MJ, Thiel KW, Leslie KK. Past, present, and future of hormonal therapy in recurrent endometrial cancer. *Int J Womens Health* 2014;6:429–435.
5. Duggan BD, Felix JC, Muderspach LI, Tourgeman D, Zheng J, Shibata D. Microsatellite instability in sporadic endometrial carcinoma. *J Natl Cancer Inst* 1994;86(16):1216–1221.
6. Risinger JI, Berchuck A, Kohler MF, Watson P, Lynch HT, Boyd J. Genetic instability of microsatellites in endometrial carcinoma. *Cancer Res* 1993;53(21):5100–5103.
7. Yeramian A, Moreno-Bueno G, Dolcet X, et al. Endometrial carcinoma: molecular alterations involved in tumor development and progression. *Oncogene* 2013;32(4):403–413.
8. Byron SA, Gartside MG, Wellens CL, et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. *Cancer Res* 2008;68(17):6902–6907.
9. Lee PS, Secord AA. Targeting molecular pathways in endometrial cancer: a focus on the FGFR pathway. *Cancer Treat Rev* 2014;40(4):507–512.
10. Byron SA, Loch DC, Pollock PM. Fibroblast growth factor receptor inhibition synergizes with paclitaxel and doxorubicin in endometrial cancer cells. *Int J Gynecol Cancer* 2012;22(9):1517–1526.
11. Dutt A, Salvesen HB, Chen TH, et al. Drug-sensitive FGFR2 mutations in endometrial carcinoma. *Proc Natl Acad Sci U S A* 2008;105(25):8713–8717.
12. Pollock PM, Gartside MG, Dejeza LC, et al. Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. *Oncogene* 2007;26(50):7158–7162.
13. Zagouri F, Bozas G, Kafantari E, et al. Endometrial cancer: what is new in adjuvant and molecularly targeted therapy? *Obstet Gynecol Int* 2010;2010:749579.
14. Okuda T, Sekizawa A, Purwosunu Y, et al. Genetics of endometrial cancers. *Obstet Gynecol Int* 2010;2010:984013.
15. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. *Cancer* 2000;88(4):814–824.
16. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013;497(7447):67–73.
17. Itoh N, Ornitz DM. Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J Biochem* 2011;149(2):121–130.
18. Greulich H, Pollock PM. Targeting mutant fibroblast growth factor receptors in cancer. *Trends Mol Med* 2011;17(5):283–292.
19. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov* 2009;8(3):235–253.
20. Holzmann K, Grunt T, Heinzle C, et al. Alternative splicing of fibroblast growth factor receptor IgIII loops in cancer. *J Nucleic Acids* 2012;2012:950508.
21. Dieci MV, Arnedos M, Andre F, Soria JC. Fibroblast growth factor receptor inhibitors as a cancer treatment: from a biologic rationale to medical perspectives. *Cancer Discov* 2013;3(3):264–279.
22. Furdui CM, Lew ED, Schlessinger J, Anderson KS. Autophosphorylation of FGFR1 kinase is mediated by a sequential and precisely ordered reaction. *Mol Cell* 2006;21(5):711–717.
23. Mohammadi M, Dionne CA, Li W, et al. Point mutation in FGF receptor eliminates phosphatidylinositol hydrolysis without affecting mitogenesis. *Nature* 1992;358(6388):681–684.

24. Hacohen N, Kramer S, Sutherland D, Hiromi Y, Krasnow MA. Sprouty encodes a novel antagonist of FGF signaling that patterns apical branching of the drosophila airways. *Cell* 1998;92(2):253–263.
25. Kovalenko D, Yang X, Nadeau RJ, Harkins LK, Friesel R. Self-inhibits fibroblast growth factor signaling by inhibiting FGFR1 tyrosine phosphorylation and subsequent ERK activation. *J Biol Chem* 2003;278(16):14087–14091.
26. Wakioka T, Sasaki A, Kato R, et al. Spred is a sprouty-related suppressor of ras signalling. *Nature* 2001;412(6847):647–651.
27. Yang RB, Ng CK, Wasserman SM, Komuves LG, Gerritsen ME, Topper JN. A novel interleukin-17 receptor-like protein identified in human umbilical vein endothelial cells antagonizes basic fibroblast growth factor-induced signaling. *J Biol Chem* 2003;278(35):33232–33238.
28. Kwabi-Addo B, Ozen M, Ittmann M. The role of fibroblast growth factors and their receptors in prostate cancer. *Endocr Relat Cancer* 2004;11(4):709–724.
29. Takahashi JA, Fukumoto M, Igarashi K, Oda Y, Kikuchi H, Hatanaka M. Correlation of basic fibroblast growth factor expression levels with the degree of malignancy and vascularity in human gliomas. *J Neurosurg* 1992;76(5):792–798.
30. Lieu C, Heymach J, Overman M, Tran H, Kopetz S. Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. *Clin Cancer Res* 2011;17(19):6130–6139.
31. Pepper MS, Ferrara N, Orci L, Montesano R. Potent synergism between vascular endothelial growth factor and basic fibroblast growth factor in the induction of angiogenesis in vitro. *Biochem Biophys Res Commun* 1992;189(2):824–831.
32. Turner N, Pearson A, Sharpe R, et al. FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. *Cancer Res* 2010;70(5):2085–2094.
33. Wang Y, Becker D. Antisense targeting of basic fibroblast growth factor and fibroblast growth factor receptor-1 in human melanomas blocks intratumoral angiogenesis and tumor growth. *Nat Med* 1997;3(8):887–893.
34. Birrer MJ, Johnson ME, Hao K, et al. Whole genome oligonucleotide-based array comparative genomic hybridization analysis identified fibroblast growth factor 1 as a prognostic marker for advanced-stage serous ovarian adenocarcinomas. *J Clin Oncol* 2007;25(16):2281–2287.
35. Giavazzi R, Sennino B, Coltrini D, et al. Distinct role of fibroblast growth factor-2 and vascular endothelial growth factor on tumor growth and angiogenesis. *Am J Pathol* 2003;162(6):1913–1926.
36. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 2005;8(4):299–309.
37. Salven P, Lymboussaki A, Heikkila P, et al. Vascular endothelial growth factors VEGF-B and VEGF-C are expressed in human tumors. *Am J Pathol* 1998;153(1):103–108.
38. Moreira IS, Fernandes PA, Ramos MJ. Vascular endothelial growth factor (VEGF) inhibition—a critical review. *Anticancer Agents Med Chem* 2007;7(2):223–245.
39. Kamat AA, Merritt WM, Coffey D, et al. Clinical and biological significance of vascular endothelial growth factor in endometrial cancer. *Clin Cancer Res* 2007;13(24):7487–7495.
40. Goel HL, Mercurio AM. VEGF targets the tumour cell. *Nat Rev Cancer* 2013;13(12):871–882.
41. Gadducci A, Sergiampietri C, Guiggi I. Antiangiogenic agents in advanced, persistent or recurrent endometrial cancer: a novel treatment option. *Gynecol Endocrinol* 2013;29(9):811–816.
42. Schmid BC, Oehler MK. Improvements in progression-free and overall survival due to the use of anti-angiogenic agents in gynecologic cancers. *Curr Treat Options Oncol* 2015;16(1):318 http://dx.doi.org/10.1007/s11864-014-0318-0.
43. Korc M, Friesel RE. The role of fibroblast growth factors in tumor growth. *Curr Cancer Drug Targets* 2009;9(5):639–651.
44. Byron SA, Gartside M, Powell MA, et al. FGFR2 point mutations in 466 endometrioid endometrial tumors: relationship with MSI, KRAS, PIK3CA, CTNNB1 mutations and clinicopathological features. *PLoS One* 2012;7(2):e30801.
45. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer: a TransPORTEC initiative. *Mod Pathol* 2015;28(6):836–844.
46. Krakstad C, Birkeland E, Seidel D, et al. High-throughput mutation profiling of primary and metastatic endometrial cancers identifies KRAS, FGFR2 and PIK3CA to be frequently mutated. *PLoS One* 2012;7(12):e52795.
47. Gatius S, Velasco A, Azueta A, et al. FGFR2 alterations in endometrial carcinoma. *Mod Pathol* 2011;24(11):1500–1510.
48. Spaans VM, Trietsch MD, Crobach S, et al. Designing a high-throughput somatic mutation profiling panel specifically for gynaecological cancers. *PLoS One* 2014;9(3):e93451.
49. Ibrahimi OA, Eliseenkova AV, Plotnikov AN, Yu K, Ornitz DM, Mohammadi M. Structural basis for fibroblast growth factor receptor 2 activation in apert syndrome. *Proc Natl Acad Sci U S A* 2001;98(13):7182–7187.
50. Ibrahimi OA, Zhang F, Eliseenkova AV, Itoh N, Linhardt RJ, Mohammadi M. Biochemical analysis of pathogenic ligand-dependent FGFR2 mutations suggests distinct pathophysiological mechanisms for craniofacial and limb abnormalities. *Hum Mol Genet* 2004;13(19):2313–2324.
51. Yu K, Herr AB, Waksman G, Ornitz DM. Loss of fibroblast growth factor receptor 2 ligand-binding specificity in apert syndrome. *Proc Natl Acad Sci U S A* 2000;97(26):14536–14541.
52. Peng WX, Kudo M, Fujii T, Teduka K, Naito Z. Altered expression of fibroblast growth factor receptor 2 isoform IIIc: Relevance to endometrioid adenocarcinoma carcinogenesis and histological differentiation. *Int J Clin Exp Pathol* 2014;7(3):1069–1076.
53. Konecny GE, Kolarova T, O'Brien NA, et al. Activity of the fibroblast growth factor receptor inhibitors dovitinib (TKI258) and NVP-BGJ398 in human endometrial cancer cells. *Mol Cancer Ther* 2013;12(5):632–642.
54. Byron SA, Chen H, Wortmann A, et al. The N550K/H mutations in FGFR2 confer differential resistance to PD173074, dovitinib, and ponatinib ATP-competitive inhibitors. *Neoplasia* 2013;15(8):975–988.
55. Fujimoto J, Hori M, Ichigo S, Tamaya T. Expression of basic fibroblast growth factor and its mRNA in uterine endometrial cancers. *Invasion Metastasis* 1995;15(5–6):203–210.
56. Soufla G, Sifakis S, Spandidos DA. FGF2 transcript levels are positively correlated with EGF and IGF-1 in the malignant endometrium. *Cancer Lett* 2008;259(2):146–155.

57. Dai H, Zhao S, Xu L, Chen A, Dai S. Expression of efp, VEGF and bFGF in normal, hyperplastic and malignant endometrial tissue. *Oncol Rep* 2010;23(3):795–799.
58. Fujimoto J, Hori M, Ichigo S, Tamaya T. Expressions of the fibroblast growth factor family (FGF-1, -2 and -4) mRNA in endometrial cancers. *Tumour Biol* 1996;17(4):226–233.
59. Harding TC, Long L, Palencia S, et al. Blockade of nonhormonal fibroblast growth factors by FP-1039 inhibits growth of multiple types of cancer. *Sci Transl Med* 2013;5(178):178ra39.
60. Harding TC, Palencia S, Long L, et al. Preclinical efficacy of FP-1039 (FGFR1:Fc) in endometrial carcinoma modelswith activating mutations in FGFR2. *AACR Annual Meeting*; 2010. Abstract 2597.
61. Ahmed Z, Schuller AC, Suhling K, Tregidgo C, Ladbury JE. Extracellular point mutations in FGFR2 elicit unexpected changes in intracellular signalling. *Biochem J* 2008;413(1):37–49.
62. Wilkie AO, Patey SJ, Kan SH, van den Ouweland AM, Hamel BC. FGFs, their receptors, and human limb malformations: clinical and molecular correlations. *Am J Med Genet* 2002;112(3):266–278.
63. Gozgit JM, Squillace RM, Wongchenko MJ, et al. Combined targeting of FGFR2 and mTOR by ponatinib and ridaforolimus results in synergistic antitumor activity in FGFR2 mutant endometrial cancer models. *Cancer Chemother Pharmacol* 2013;71(5):1315–1323.
64. Powell MA, Sill MW, Goodfellow PJ, et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG oncology/gynecologic oncology group study. *Gynecol Oncol* 2014;135(1):38–43.
65. Dizon DS, Sill MW, Schilder JM, et al. A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: an NRG oncology/gynecologic oncology group study. *Gynecol Oncol* 2014;135(3):441–445.
66. Konecny GE, Finkler N, Garcia AA, et al. Phase 2 study of second-line dovitinib (TKI258) in patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or -nonmutated advanced and/or metastatic endometrial cancer. *Eur Soc Med Oncol* 2014. [Abstract LBA27].
67. Konecny GE, Finkler N, Garcia AA, et al. Second-line dovitinib (TKI258) in patients with FGFR2-mutated or FGFR2-non-mutated advanced or metastatic endometrial cancer: A non-randomised, open-label, two-group, two-stage, phase 2 study. *Lancet Oncol* 2015;16(6):686–694.
68. Hong DS, Kurzrock R, Wheler JJ, et al. Phase I dose-escalation study of the multikinase inhibitor lenvatinib in patients with advanced solid tumors and in an expanded cohort of patients with melanoma. *Clin Cancer Res* 2015;21(21) 4801–4810.
69. Vergote I, Teneriello M, Powell MA, et al. A phase II trial of lenvatinib in patients with advanced or recurrent endometrial cancer: angiopoietin-2 as a predictive marker for clinical outcomes. *J Clin Oncol* 2013;31(suppl). [ASCO Annual Meeting Abstracts, Abstract 5520].
70. Funahashi Y, Penson RT, Powell MA, et al. Analysis of plasma biomarker and tumor genetic alterations from a phase II trial of lenvatinib in patients with advanced endometrial cancer. *J Clin Oncol* 2013;31(suppl). [ASCO Annual Meeting Abstracts, Abstract 5591].
71. Gozgit JM, Wong MJ, Moran L, et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol Cancer Ther* 2012;11(3):690–699.
72. Castonguay V, Lheureux S, Welch S, et al. A phase II trial of sunitinib in women with metastatic or recurrent endometrial carcinoma: a study of the princess margaret, chicago and california consortia. *Gynecol Oncol* 2014;134 (2):274–280.
73. Nimeiri HS, Oza AM, Morgan RJ, et al. A phase II study of sorafenib in advanced uterine carcinoma/carcinosarcoma: a trial of the chicago, PMH, and california phase II consortia. *Gynecol Oncol* 2010;117(1):37–40.
74. McMeekin DS, Sill MW, Benbrook D, et al. A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a gynecologic oncology group study. *Gynecol Oncol* 2007;105 (2):508–516.
75. McMeekin DS, Sill MW, Darcy KM, et al. A phase II trial of thalidomide in patients with refractory uterine carcinosarcoma and correlation with biomarkers of angiogenesis: a gynecologic oncology group study. *Gynecol Oncol* 2012;127(2):356–361.
76. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a gynecologic oncology group study. *J Clin Oncol* 2011;29(16):2259–2265.
77. Alvarez EA, Brady WE, Walker JL, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a gynecologic oncology group study. *Gynecol Oncol* 2013;129(1):22–27.
78. Coleman RL, Sill MW, Lankes HA, et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: a gynecologic oncology group study. *Gynecol Oncol* 2012;127(3):538–543.
79. Wilkie AO, Slaney SF, Oldridge M, et al. Apert syndrome results from localized mutations of FGFR2 and is allelic with crouzon syndrome. *Nat Genet* 1995;9(2):165–172.
80. Li Y, Mangasarian K, Mansukhani A, Basilico C. Activation of FGF receptors by mutations in the transmembrane domain. *Oncogene* 1997;14(12):1397–1406.
81. Lorenzi MV, Castagnino P, Chen Q, Chedid M, Miki T. Ligand-independent activation of fibroblast growth factor receptor-2 by carboxyl terminal alterations. *Oncogene* 1997;15(7):817–826.