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Molecular Case Studies

RESEARCH REPORT

Comprehensive genomic profiling aids in treatment of a metastatic endometrial cancer

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Abstract *FGFR-TACC* fusions, including *FGFR3-TACC3*, have been identified as potential oncogenic drivers and actionable alterations in a number of different cancer types. The clinical relevance of *FGFR3-TACC3* fusions in endometrial cancer has not yet been described. Formalin-fixed, paraffin-embedded metastatic endometrial carcinoma from the spleen and peritoneum were sent for comprehensive genomic profiling (CGP) using the FoundationOne platform as part of a prospective tumor genomic profiling protocol. We report the identification of an *FGFR3-TACC3* fusion in a case of metastatic endometrioid endometrial cancer. Other potentially actionable alterations detected in this specimen included *PIK3CA* T1025S and an uncharacterized rearrangement involving *TSC2*. The patient initially received an FGFR inhibitor as an investigational agent and experienced stable disease with complete resolution of a pelvic nodule; however, treatment had to be discontinued because of intolerable side effects. A PET/CT scan nearly 3 mo after discontinuation showed disease progression. She subsequently received the mTOR inhibitor, temsirolimus, later accompanied by letrozole, and achieved stable disease. Clinical benefit was attributed to the mTOR inhibitor as tumor stained negative for estrogen receptor. Temsirolimus was discontinued after >17 mo because of disease progression. FGFR inhibitors may have clinical benefit in the treatment of endometrial carcinoma with *FGFR3-TACC3* fusions. Additionally, clinical benefit from an mTOR inhibitor may reflect a response to targeting the alteration in *PIK3CA* or *TSC2*. More research is needed to understand the activity of *FGFR3-TACC3* fusions on tumors and to discover additional therapeutic options for endometrial carcinoma patients with this gene fusion.

[Supplemental material is available for this article.]

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INTRODUCTION

Significant progress in the development of comprehensive genomic profiling (CGP) platforms, analyses, and targeted therapies has culminated in the use of these modalities to reclassify and to treat many cancers, including endometrial carcinoma. Endometrial cancer, the most common gynecologic cancer, is predicted to account for 61,380 new cases of gynecologic cancers affecting women in the United States in 2017 (Siegel et al. 2016). Risk factors of endometrial cancer include obesity, diabetes mellitus, high blood pressure, tamoxifen treatment, and unopposed estrogen use (McConechy et al. 2012; Trabert et al. 2015; Morice et al. 2016). Current treatment modalities for women with endometrial cancer are surgery or surgery in combination with radiation therapy and/or chemotherapy, hormone therapy, and biologic therapy (National Cancer Institute 2002; National Comprehensive Cancer Network 2014). However, prognosis is worsened for women with recurrent or metastatic disease, as treatment options are limited and suboptimal (Temkin and Fleming 2009; Rauh-Hain and Del Carmen 2010; Lee and Secord 2014).

Advances in molecular genotyping have not only identified molecular heterogeneity driving tumor behavior (The Cancer Genome Atlas Research Network et al. 2013) but have also shed light on alternative approaches to therapeutically target tumors with specific mutations (Conley 2015; Meric-Bernstam et al. 2015; Tobin et al. 2015). Common alterations seen in endometrial cancers include mutations in the PI3K pathway (occurring in >80% of the endometrioid subtype) (Cheung et al. 2011), copy-number alterations (frequently observed in serous and mixed histology endometrial cancers, but also seen in endometrioid endometrial cancers; seen in such genes as *ERBB2*, *FGFR3*, and *CCNE1*), and frequent *TP53* mutations (The Cancer Genome Atlas Research Network et al. 2013). *FGFR* alterations reported in endometrial cancers most frequently involve *FGFR2* (Helsten et al. 2016). According to The Cancer Genome Atlas (TCGA) for data reported in *Nature* in 2013, the most frequently altered *FGFR* gene in endometrial cancers was *FGFR2*, with 12.5% of sequenced samples ($n = 248$ samples) harboring alterations in this gene. Gene fusions in endometrial cancers, although less common than copy-number alterations and point mutations, involve members of various pathways with recurrent translocations that most frequently involve genes of the BCL-2 family, followed by PI3K, WNT, EGFR, RAS–MAPK, protein kinase A, and retinoblastoma pathways (The Cancer Genome Atlas Research Network et al. 2013).

We report on a woman with a platinum-resistant recurrence of a metastatic endometrioid endometrial carcinoma with poorly differentiated, widespread carcinomatosis and splenic involvement. CGP performed on a tumor specimen revealed several potentially actionable alterations, including both an *FGFR3-TACC3* fusion and a *PIK3CA*-activating mutation. Consensus opinion from our institutional molecular tumor board (MTB) led to enrollment of this patient on a clinical trial including an FGFR inhibitor and subsequent therapy with an mTOR inhibitor, to which she derived a prolonged clinical benefit. This case demonstrates the utility of tumor genomic profiling with the ability to identify gene rearrangements as a method of identifying potentially actionable targets in endometrial cancers.

RESULTS

Clinical Presentation and Family History

A 57-yr-old nulliparous, postmenopausal female presented with intermittent abnormal vaginal bleeding over 3 yr. Her history was significant for menarche at age 11, menopause at age 50, diabetes managed with metformin, body mass index of 29, and a remote 40 pack/year smoking history where tobacco cessation occurred 20 yr prior to diagnosis. She had no

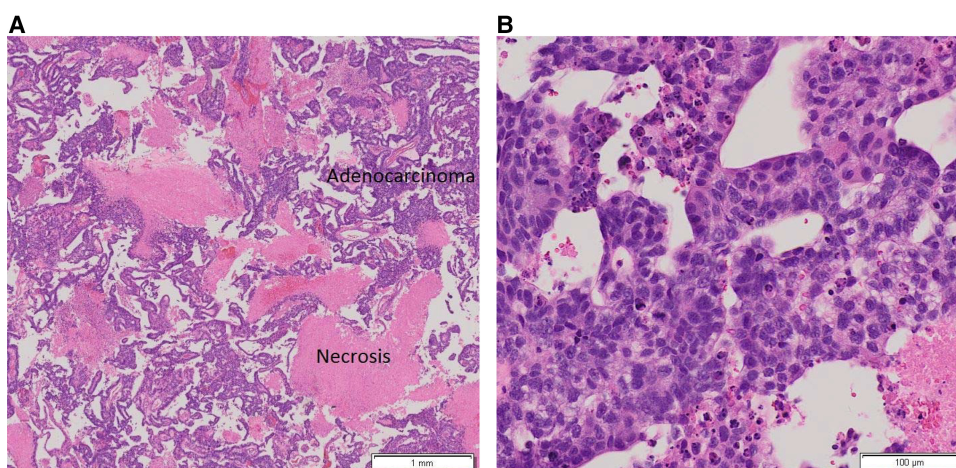

Figure 1. Hematoxylin and eosin (H&E)-stained endometrial biopsy showing endometrial adenocarcinoma with papillary features and necrosis at low (*A*) and high (*B*) magnification, respectively.

history of exogenous hormone use. She had a dilation and curettage 3 yr prior to the initial cancer diagnosis that showed no pathology. The patient continued to experience abnormal vaginal bleeding, and a second endometrial biopsy revealed moderately differentiated endometrioid adenocarcinoma, FIGO grade II, with extensive necrosis (Fig. 1A,B).

She underwent an exploratory laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathology confirmed a high-grade, 8.5 cm × 8 cm × 5 cm endometrioid adenocarcinoma, FIGO grade II, with extensive necrosis and focal clear cell changes. There was <10% myometrial invasion. No lymphovascular invasion or cervix involvement was noted. Eighteen pelvic and para-aortic lymph nodes showed no metastases. Final staging was 1A (pT1a, N0), based on the 2009 FIGO staging guidelines. Because she had a high risk for recurrence, the patient received whole pelvis radiation therapy and brachytherapy on a clinical trial that was completed 9 mo prior to the presentation of recurrent disease.

A CT scan of the abdomen and pelvis following completion of radiation showed stable hypodensities in the liver that were too small to characterize. However, 9 mo after completion of the trial, a follow-up CT scan showed a new 8-mm hypodense lesion in the splenic hilum and ring-like enhancement along the posterior margin of spleen not seen on the previous exam. A subsequent PET-CT scan revealed two abnormal hypermetabolic foci in the spleen (SUV 3.2 in the hilum, SUV 4.5 in a 1.2 cm hypodense lesion), stable non-FDG-avid liver lesions, and no pelvic adenopathy. The patient underwent splenectomy, and pathology was consistent with metastasis of the original tumor to the spleen (Fig. 2A,B). She received six cycles of intravenous carboplatin (AUC = 5) in combination with paclitaxel (175 mg/m^2). Nearly 14 mo later, a CT scan of the chest, abdomen, and pelvis (CAP) revealed an increase in the size of previously visualized abdominal nodules, which were now suspicious for peritoneal carcinomatosis. A fine needle aspiration of the nodules within the abdomen and pelvis confirmed adenocarcinoma with extensive necrosis. A diagnostic laparoscopy was performed to resect tumor nodules (Fig. 3A,B), which were then sent for comprehensive tumor genomic profiling (CGP) under the auspices of a clinical trial.

Genomic Analyses

The patient provided informed consent to participate in the Rutgers CINJ genomic tumor profiling protocol (NCT02688517), which was approved by the Institutional Review Board (IRB) of Rutgers University New Brunswick Health Sciences (Pro2012002075). The specimen from the patient's laparoscopy underwent CGP using the FoundationOne platform, which

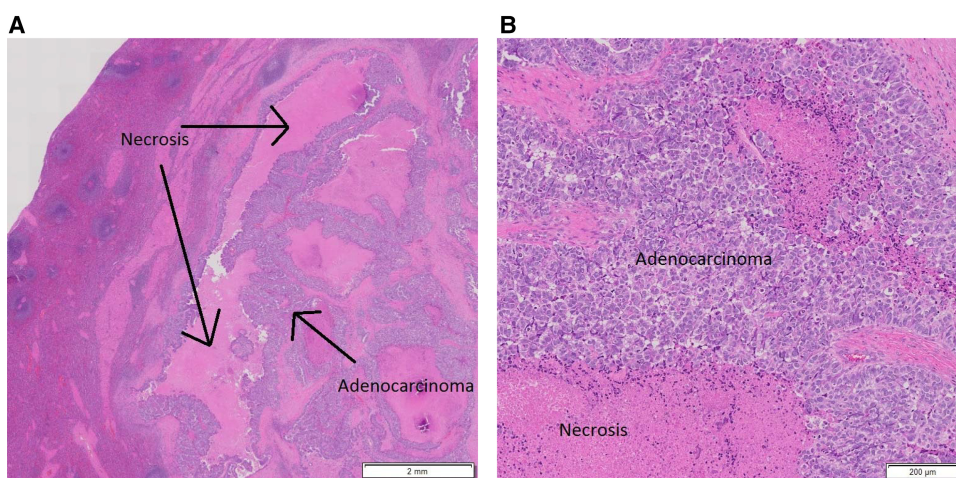

Figure 2. H&E-stained slide of tissue from splenectomy showing metastatic, moderately differentiated adenocarcinoma with necrosis at low (*A*) and high (*B*) magnification, respectively.

consisted of whole-exon sequencing of a panel of 236 genes and 47 introns of 19 genes involved in translocations. Tumor genomic profiling revealed an *FGFR3-TACC3* fusion (breakpoints at FGFR3 exon 17 and TACC3 exon 8), a missense mutation in *PIK3CA* (T1025S), and an uncharacterized rearrangement involving *TSC2* (Table 1). A subthreshold amplification of the entire coding region of *FGFR3* (copy number 6) was also detected, further validating the rearrangement. The results of tumor genomic profiling, clinical course, and pathology were reviewed at the Rutgers Cancer Institute of New Jersey Molecular Tumor Board (RCINJ MTB).

Data suggest that *FGFR3* fusion-containing cells are addicted to FGFR kinase activity and are sensitive to FGFR pan-inhibitors, such as pazopanib and PD173074 (Pollock et al. 2007; Lamont et al. 2011; Dieci et al. 2013; Williams et al. 2013). Given the preclinical study results, MTB recommendations to the treating oncologist included consideration of a trial using an FGFR inhibitor, a phase I trial of the combination carboplatin/paclitaxel/pazopanib, a trial with a PIK3CA inhibitor, an mTOR inhibitor, and off-label use of ponatinib or pazopanib.

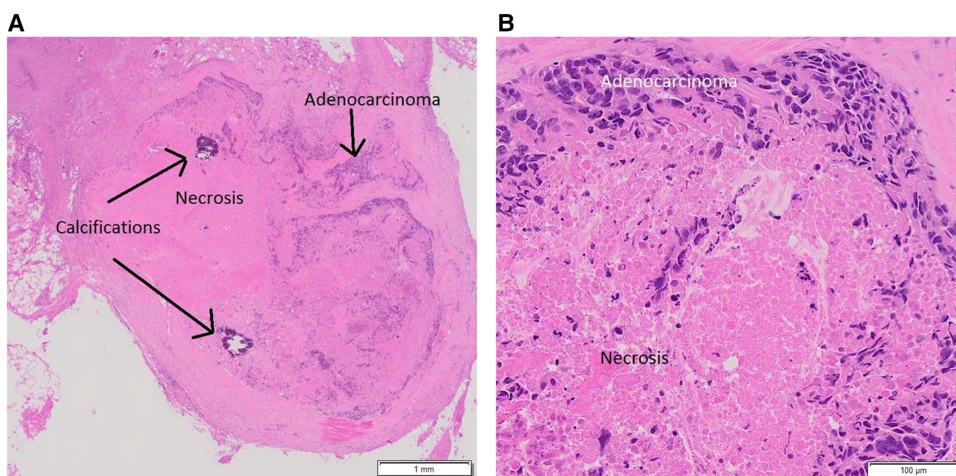

Figure 3. H&E-stained slide showing metastatic adenocarcinoma with necrosis and calcifications following diagnostic laparoscopy with removal of the anterior abdominal wall nodule at low (*A*) and high (*B*) magnification, respectively; specimen from this procedure was sent for comprehensive genomic profiling.

Table 1. Variants identified from comprehensive genomic profiling

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect
FGFR3	4	t(4;4) Chr 4 duplication fragment: 5′-*FGFR3* (ex1-17 NM_000142)-*TACC3* (ex8-16 NM_006342) Breakpoints: *FGFR3* exon 17, *TACC3* exon 8	N/A	Fusion	Functional
PIK3CA	3	N/A	p.T1025S	Substitution	Predicted functional
TSC2	16	t(16;16) ~206-kbp duplication fragment: 3′-*TSC2* (NM_000548), Breakpoints: *TSC2* exon 26, *ABCA3* intron 25	N/A	Fusion	Unknown

Targeted sequencing of the entire coding sequence was done for 236 genes and 47 introns of 19 genes involved in fusions at a depth of 500–1000× (median exon depth of 792×; 100% of the baited region was sequenced at a depth of at least 100×; sequence alignment error of only 0.27%). The depth of variant call reads was 59×; these 59 chimeric reads equate to an independently validated variant calling method described in Frampton et al. (2013). The depth of wild-type reads was 1155×.
HGVS, Human Genome Variation Society; N/A, not available.

Intriguingly, several variants of unknown significance were also reported in the tumor of this patient and included a *TSC2* rearrangement. The *TSC2* rearrangement was a 3′ tandem duplication of *TSC2* with breakpoints in exon 26 and *ABCA3* intron 25. This is an out of strand fusion event, because *TSC2* and *ABCA3* are transcribed in the positive and negative directions, respectively. The reciprocal event was not seen for this rearrangement. Additionally, there was a subthreshold amplification in *TSC2* exons 26–42 (copy number 7) that further validate the rearrangement.

Treatment Outcomes

The patient was enrolled into a phase I clinical trial with an FGFR inhibitor. This MTB recommendation was based on the inference that the *FGFR3-TACC3* fusion-containing tumor would be addicted to FGFR kinase activity. The patient experienced stable disease over the course of nearly 2 mo with complete resolution of a pelvic nodule, as observed in CT scans (Fig. 4A–D). However, at nearly four full cycles, the patient was removed from the study for grade 3 palmar-plantar erythrodysesthesia. The patient showed disease progression on a PET/CT scan about 3 mo following cessation of the FGFR inhibitor on trial (Fig. 5A–D).

The patient was subsequently treated with the mTOR inhibitor temsirolimus based on recommendations from the MTB as an inferred downstream target of the *PIK3CA* alteration. Recommendations were not based on the *TSC2* alteration, as this was a variant of unknown significance. She received temsirolimus for >17 mo with a few instances of the drug being withheld because of fever and neuropathy. Because of stable disease after >8 mo with foci showing mixed response and evidence from the treatment of breast cancer that mTOR inhibitors enhance the response to antiestrogen therapy, letrozole (2.5 mg/d orally) was added to the weekly regimen of temsirolimus (Baselga et al. 2009; Liu et al. 2014). The patient continued on temsirolimus and letrozole for nearly 9 additional months until disease progression was detected.

DISCUSSION

The FGFR family is made up of four active members, *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4* (Turner and Grose 2010). Alterations in these genes, such as amplifications, mutations, or translocations, may lead to the constitutive or increased activation of the tyrosine kinases in their protein products (Dutt et al. 2008; Turner and Grose 2010; Singh et al. 2012). Both in vitro and in vivo studies on cancer cells and tumors containing FGFR fusions suggest

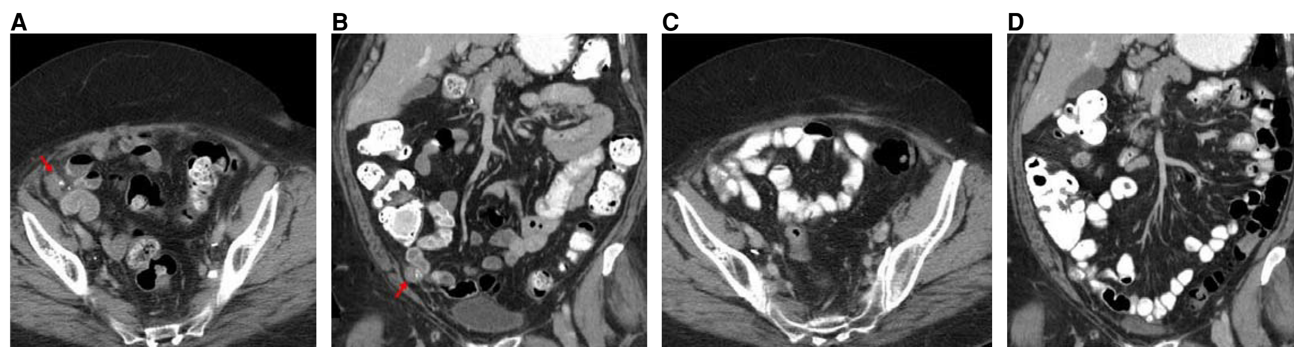

Figure 4. CT scans of the abdomen and pelvis with contrast prior to initiation of an FGFR inhibitor on trial. (*A*) Axial CT image with oral and intravenous contrast at the level of the mid pelvis shows a 3-cm soft tissue mass with minimal calcifications (red arrow). (*B*) Coronal reconstructed CT image with oral and intravenous contrast through the anterior abdomen and pelvis shows the 3-cm soft tissue mass with minimal calcifications (red arrow). CT scans of the abdomen and pelvis with contrast obtained during treatment with FGFR inhibitor on trial. (*C*) Axial CT image with oral and intravenous contrast at the level of the mid pelvis shows no measurable mass. (*D*) Coronal reconstructed CT image with oral and intravenous contrast through the anterior abdomen and pelvis shows no measurable mass.

oncogenic potential and, therefore, potential growth impairment with FGFR-specific and pan-kinase inhibitors for different tumor subtypes.

Because of the unusual presentation of recurrent endometrial cancer affecting the spleen, CGP was performed on the tumor in the aforementioned case. This revealed that the tumor contained an *FGFR3-TACC3* fusion and a missense mutation in *PIK3CA* (Table 1). *TACC3*, or transforming acidic coiled-coil containing protein 3, is involved in

Figure 5. CT scans of the abdomen and pelvis with contrast shortly following discontinuation of trial with FGFR inhibitor. (*A*) Axial CT image shows no measurable mass. (*B*) Coronal reconstructed CT image shows no measurable mass. PET/CT scans 3 mo following cessation of the FGFR inhibitor on trial. (*C*) Axial CT image without oral or intravenous contrast at the mid pelvis shows a 3-cm mass with calcifications. (*D*) PET scan with coronal display shows an area of increased abnormal metabolic activity corresponding to the soft tissue mass (red arrow).

mitotic spindle organization and possible stemness properties of cells (Zhou et al. 2015). It is positioned on Chromosome 4 upstream of *FGFR3*. The *FGFR3-TACC3* fusion event is believed to occur through a tandem duplication of a region of the chromosome where both genes exist, 4p16.3 (Parker et al. 2013). The fusion event, through the help of the coiled-coil domain on *TACC3*, increases autophosphorylation of tyrosine residues on the FGFR3 kinase domain and leads to a constitutively active FGFR3 protein (Fig. 6; Nelson et al. 2016). The frequency of alterations in uterine cancer for the genes altered in our patient case was reported by The Cancer Genome Atlas (TCGA) (Fig. 7; Cerami et al. 2012; Gao et al. 2013).

Alterations, including amplifications, deletions, and missense and nonsense mutations in *FGFR* genes, have previously been observed in endometrial cancers (Pollock et al. 2007; Dutt et al. 2008; Byron et al. 2012; Konecny et al. 2013; Helsten et al. 2016). Although the most frequently altered *FGFR* gene was *FGFR2*, with ~15% of cases according to TCGA data, alterations in *FGFR1*, *FGFR3*, and *FGFR4* have also been observed at a frequency of 6%, 5%, and 5%, respectively, in endometrial cancers (Fig. 8; Cerami et al. 2012; Gao et al. 2013).

FGFR fusions, including *FGFR-TACC* fusions, have been observed among a variety of cancer types. For example, *FGFR3-TACC3* fusions have been reported in a subset of bladder cancer (Williams et al. 2013; Wu et al. 2013), low-grade glioma (Granberg et al. 2017), glioblastoma (independently identified and reported by Singh et al. 2012 and Parker et al. 2013), nasopharyngeal carcinoma (Yuan et al. 2014), cervical cancer (Carneiro et al. 2015), head and neck squamous cell carcinoma (Wu et al. 2013), lung squamous cell carcinoma (Wu et al. 2013), and oral cancer (Wu et al. 2013). Helsten et al. (2016) reviewed the genomic profiling of nearly 5000 tumor samples from a variety of cancer types. They found one case out of 80 cases of endometrial cancer with an *FGFR3-TACC3* fusion (Helsten et al. 2016). Additionally, data from Foundation Medicine, Inc. found four cases of endometrial cancer that contained an *FGFR3-TACC3* fusion. Among 813 patients with endometrial adenocarcinoma (NOS), two patients (0.25%) had an *FGFR3-TACC3* fusion. One of these patients included the patient featured in our case study. Additionally, one out of 64 patients (1.60%) with

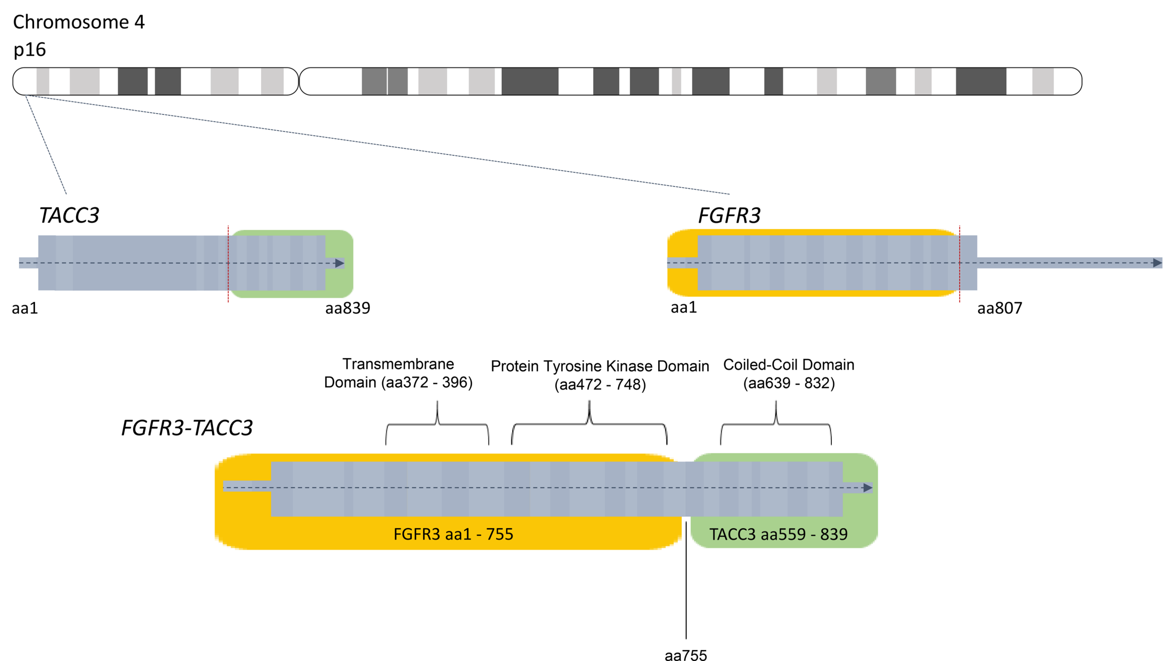

Figure 6. Diagram of the formation of the FGFR3-TACC3 fusion protein product.

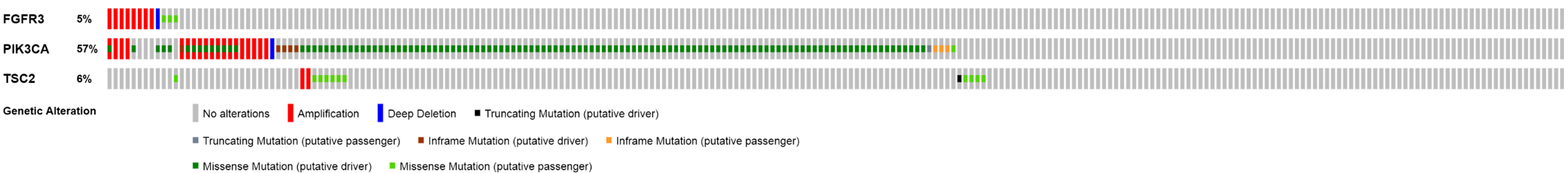

Figure 7. Frequency of alterations found in *FGFR3*, *PIK3CA*, or *TSC2* reported in uterine corpus endometrial carcinoma (TCGA Provisional) for 242 cases. The results shown here are based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/.

Figure 8. Percentages of uterine cancer cases with alterations in *FGFR* genes, as reported by TCGA for 242 cases (TCGA Provisional). The results shown here are based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/.

Table 2. Descriptions of the genomic breakpoints for the patients provided by Foundation Medicine, Inc.

Disease ontology[a]	Genomic breakpoints
Uterus endometrial adenocarcinoma (NOS)	Chr 4 duplication fragment: 5′-*FGFR3*(ex1-18 UTR NM_000142)-*TACC3*(ex10-16 NM_006342) Breakpoints *FGFR3* exon 18, *TACC3* intron 9
[a]Uterus endometrial adenocarcinoma (NOS)	Chr 4 duplication fragment: 5′-*FGFR3*(ex1-17 NM_000142)-*TACC3*(ex8-16 NM_006342) Breakpoints *FGFR3* exon 17, *TACC3* exon 8
Uterus endometrial adenocarcinoma clear cell	Chr 4 duplication fragment: 5′-*FGFR3*(ex1-2 NM_000142)-*TACC3*(ex7-16 NM_006342) Breakpoints *FGFR3* exon 2, *TACC3* intron 6
Uterus endometrial adenocarcinoma papillary serous	Chr 4 duplication fragment: 5′-*FGFR3*(ex1-18 UTR NM_000142)-*TACC3*(ex10-16 NM_006342) Breakpoints *FGFR3* exon 18, *TACC3* intron 9

[a]Highlighted case results.

clear cell endometrial adenocarcinoma and one out of 419 patients (0.24%) with papillary serous endometrial adenocarcinoma had an *FGFR3-TACC3* fusion. These data highlight the unique nature of these fusions in endometrial cancers. Details on the genomic breakpoints involved in these fusions are listed in Table 2. Our case sheds additional light on this rare but significant fusion event in endometrial cancer and follows the patient through treatment with targeted therapy.

Di Stefano et al. (2015) illustrated differential effectiveness of the FGFR inhibitor JNJ-42756493 on mouse astrocytes and human glioma stem cells expressing the *FGFR3-TACC3* gene fusion versus similar cells lacking this fusion. The authors reported on two patients with recurrent glioblastoma who were found to have *FGFR3-TACC3* fusions (breakpoints: *FGFR3* exon 17 and *TACC3* exon 6; *FGFR3* exon 17 and *TACC3* exon 8). Following treatment with the FGFR inhibitor JNJ-42756493 in the context of a clinical trial, stabilization of disease was observed for ∼16 and ∼19 wk, respectively, where 2 wk was equivalent to one cycle. Progression of disease was subsequently observed (Di Stefano et al. 2015). This drug has also been shown to lead to partial responses in patients with an *FGFR3-TACC3*-containing urothelial cancer and a decrease in tumor size in a patient with an adrenal cancer harboring this fusion (Tabernero et al. 2015).

Before developing toxicity, the patient in the present report was benefiting from the FGFR inhibitor within the context of a clinical trial. Other FGFR-specific inhibitors have been developed, though none has yet been FDA-approved for the treatment of solid tumors. The FGFR inhibitor PD173074 reduced the viability of nasopharyngeal carcinoma cells harboring a *FGFR3-TACC3* fusion in a dose-dependent manner (Yuan et al. 2014). FGFR3-TACC3 showed constitutive FGFR kinase activity, followed by the inhibition of this activity with PD173074 in transduced human astrocytes and mouse glioma stemlike cells (Singh et al. 2012). NVP-BGJ398 demonstrated FGFR1-4 inhibition in human embryonic kidney cells (Guagnano et al. 2011), whereas LY2874455 exhibited inhibition of FGFR2 in human gastric carcinoma cell lines (Zhao et al. 2011). These studies and our present case provide the rationale for considering FGFR inhibitors for patients whose tumor genomic profiles indicate this fusion. More research is needed to understand the activity of *FGFR3-TACC3* fusions on tumors and, consequently, to discover additional clinically relevant therapeutic options for endometrial cancer patients with this gene fusion.

This patient's tumor also harbored a *PIK3CA* mutation, which is another putative targetable alteration. *PIK3CA* is a gene encoding for a catalytic subunit within the PI3K molecule (Volinia et al. 1994). Alterations in *PIK3CA* are implicated in 41%–52% of endometrioid endometrial carcinomas and between 33% and 38% of nonendometrioid endometrial carcinomas (e.g., papillary serous histology, clear cell histology) (Slomovitz and Coleman 2012). PI3K inhibitors, although still experimental or in clinical trials, have been developed (Khan et al. 2013).

Tumors harboring *PIK3CA* mutations may benefit from mTOR inhibitors, as mTOR is a target downstream from PI3K (Khan et al. 2013). mTOR inhibitors are a class of drugs that target mutations in the PI3K/AKT/mTOR pathway and limit both tumor cell proliferation and progression through the cell cycle (Husseinzadeh and Husseinzadeh 2014). The predictive value of a *PIK3CA* mutation for mTOR inhibitor response has been inconsistent across tumor types. Other alterations in this tumor may account for drug response. For example, this tumor also carried a *TSC2* rearrangement with a breakpoint in exon 26 but was reported as a variant of unknown significance. Germline mutations in *TSC2* result in developmental defects seen in tuberous sclerosis (Jones et al. 1997; Dabora et al. 2001; Langkau et al. 2002). Although tuberous sclerosis is an autosomal dominant disease, the hamartomatous growths associated with this disease often include the loss of heterozygosity of *TSC2* (or, less commonly, TSC1) (Carbonara et al. 1996; Kwiatkowski 2003). It is not known if this tumor displays loss of heterozygosity. This alteration disrupts TSC2 upstream of the GTPase-activating protein (GAP)-related domain (exons 34–38) and may confer relevant loss of function (Maheshwar et al. 1997). With loss-of-function mutations in *TSC2*, the protein is phosphorylated and inhibited by AKT, stimulating Rheb GTPase activity, and leading to the activation of mTOR (Maheshwar et al. 1997; Kwiatkowski 2003; Li et al. 2004; Dibble and Cantley 2015; Huynh et al. 2015). Exceptional responses have been observed in patients with otherwise aggressive, *TSC2*-mutated tumors with mTOR inhibitor therapy (Wagle et al. 2014). Because retrospective analysis of this tumor did not reveal expression of estrogen receptor (not shown), the 17-mo clinical benefit experienced by this patient was likely due to mTOR inhibition. The observed clinical benefit strongly implicates the *TSC2* rearrangement as being functional, although a benefit due to other upstream alterations cannot be ruled out.

METHODS

This patient was evaluated at the Rutgers CINJ and provided informed consent to participate in a prospective study trial for tumor genomic profiling (NCT02688517). This trial was approved by the Rutgers University New Brunswick Health Sciences IRB (Pro2012002075). Clinical records were abstracted for relevant patient history and tumor characteristics; data were abstracted until the end of October 2015, therefore, subsequent data were not reflected in this manuscript. Medical history, pathology, radiology, clinical course, and genomic profiling results were reviewed in an anonymized fashion at a formal MTB. Profiling results were discussed in the context of clinical course, tumor type, mutational frequency, role in cell pathways contributing to cancer biology, and considerations for future therapy including consensus recommendations for clinical trials, FDA-approved therapies (on or off label), and genetic counseling, if appropriate. The patient was followed prospectively for clinical course. The protocol for tumor genomic profiling was approved by the Institutional Review Board of Rutgers Robert Wood Johnson Medical School.

For the additional patients provided by Foundation Medicine, Inc., approval for this study, including a waiver of informed consent and a HIPAA waiver of authorization, was obtained from the Western Institutional Review Board (Protocol No. 20152817).

Comprehensive Genomic Profiling

Details on the sequencing methodology used in this study can be found in Frampton et al. (2013). Routine formalin-fixed, paraffin-embedded (FFPE) tissue was sent to Foundation Medicine, Inc. for CGP using the CLIA-certified FoundationOne platform (Frampton et al. 2013). Targeted sequencing of the entire coding sequence was done for 236 genes and 47 introns of 19 genes involved in fusions at a depth of 500×–1000× (median exon depth of 792×; 100% of the baited region was sequenced at a depth of at least 100×; sequence

alignment error of only 0.27%). The depth of variant call reads was 59×; these 59 chimeric reads equate to an independently validated variant calling method described in Frampton et al. (2013). The depth of wild-type reads was 1155× (please see Supplemental Table S1).

Pathology

H&E-stained slides of tissue samples at various time points in the clinical care of the case patient were reviewed by Pathology.

Radiology

CT scans of the abdomen and pelvis (axial and coronal reconstructed), with or without oral/intravenous contrast, were performed at various time points in the clinical care of the case patient. A PET scan with coronal display was also performed. The scans were reviewed by J.K.A. and L.R.-R. RECIST criteria were used to determine response based on CT scan imaging (Eisenhauer et al. 2009).

ADDITIONAL INFORMATION

Data Deposition and Access

The genomic variants for our patient case were deposited into ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession numbers SCV000693748–SCV000693750.

Ethics Statement

The patient provided informed consent to participate in the Rutgers CINJ genomic tumor profiling protocol (NCT02688517), which was approved by the Institutional Review Board (IRB) of Rutgers University New Brunswick Health Sciences (Pro2012002075).

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Author Contributions

J.D. contributed to manuscript preparation; K.M.H. contributed to genomic data interpretation and manuscript preparation; S.G. contributed to genomic data interpretation and manuscript preparation; M.H. contributed to patient care and manuscript preparation; V.R. contributed to manuscript preparation; J.K.A. contributed to manuscript preparation and data interpretation; G.M.R. contributed to manuscript preparation and data interpretation; H.Z. contributed to manuscript preparation and data interpretation; S.M.A. contributed to comprehensive genomic profiling, data analysis, and manuscript preparation; D.P. contributed to comprehensive genomic profiling, data analysis, and manuscript preparation; J.A.E. contributed to comprehensive genomic profiling, data analysis, and manuscript preparation; L.R.-R. contributed to patient care, genomic data interpretation, and manuscript preparation.

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Competing Interest Statement

S.G. serves on a scientific advisory board and as consultant to Inspirata, Inc., and has equity in Inspirata, Inc.; serves on an advisory board for Novartis Pharmaceuticals; and has patents on digital imaging technology licensed to Inspirata, Inc. S.M.A. is an employee of Foundation Medicine Inc. D.P. is an employee of Foundation Medicine Inc. J.A.E. is an employee of Foundation Medicine Inc.

Referees

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