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A Phase II Trial of Brivanib in Recurrent or Persistent Endometrial Cancer: An NRG Oncology/Gynecologic Oncology Group Study

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Abstract

Purpose—Brivanib, an oral, multi-targeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor (FGFR) was

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CONFLICT OF INTEREST

Dr. Matthew Powell is a consultant for Genentech, Eisai, and Arno Therapeutics.

Dr. Doris Benbrook received payment for consulting service as a Scientific Expert Witness in a bexarotene patent litigation case by Banner Pharmacaps Inc. and Mylan Inc. through Haynes and Boone, LLC. Travel during this service was reimbursed.

Dr. Pamela Pollock is a member of advisory board for Phase III trial planning for Doritinib (travel and accommodations paid for by Novartis).

investigated as a single agent in a phase II trial to assess the activity and tolerability in recurrent or persistent endometrial cancer (EMC).

Patients and Methods—Eligible patients had persistent or recurrent EMC after receiving one to two prior cytotoxic regimens, measurable disease, and performance status of 2. Treatment consisted of brivanib 800 mg orally every day until disease progression or prohibitive toxicity. Primary endpoints were progression-free survival (PFS) at six months and objective tumor response. Expression of multiple angiogenic proteins and FGFR2 mutation status was assessed.

Results—Forty-five patients were enrolled. Forty-three patients were eligible and evaluable. Median age was 64 years. Twenty-four patients (55.8%) received prior radiation. Median number of cycles was two (range 1–24). No GI perforations but one rectal fistula were seen. Nine patients had grade 3 hypertension, with one experiencing grade 4 confusion. Eight patients (18.6%; 90% CI 9.6–31.7%) had responses (one CR and seven PRs), and 13 patients (30.2%; 90% CI 18.9–43.9%) were PFS at six months. Median PFS and overall survival (OS) were 3.3 and 10.7 months, respectively. When modeled jointly, VEGF and Angiopoietin-2 expression may diametrically predict PFS. Estrogen receptor- α (ER) expression was positively correlated with OS.

Conclusion—Brivanib is reasonably well tolerated and worthy of further investigation based on PFS at six months in recurrent or persistent EMC.

Keywords

Brivanib; endometrial cancer

INTRODUCTION

Endometrial cancer (EMC) is the most common gynecologic malignancy in the United States and represents the vast majority (90%) of uterine corpus cancers [1]. In 2014 The American Cancer Society estimates 49,560 new cases of cancer of the uterine corpus with 8,190 women dying [2]. The median survival after recurrence is 10 months and the five-year survival for patients who have recurred is <15%. Therapies (radiation, hormonal, chemotherapy, or combinations) for women with advanced stage, progressive or recurrent EMC are not very effective and novel therapies are desperately needed.

There have been several randomized studies addressing the issue of optimal therapy for this group of patients. A recently reported study randomly assigned 1350 patients to paclitaxel, doxorubicin, and cisplatin (TAP) versus carboplatin and paclitaxel (TC) to determine if TC is therapeutically equivalent. They found that TC is not inferior to TAP in terms of progression-free survival (PFS) and overall survival (OS) based on interim analysis results and the toxicity profile favors TC [3]. Once this initial therapy has been delivered, there are limited treatment options. Although hormonal therapies can result in responses and improved PFS, most often these responses are of short duration [4–5]. Other targeted therapies have been, or are currently being tested, but have yet to be implemented into routine clinical practice. The majority of completed endometrial cancer studies with targeted agents demonstrated minimal to modest activity including: agents that target vascular endothelial growth factors and receptors (VEGF(R))-sunitinib, sorafenib, and thalidomide; human epidermal growth factor receptor 1 and 2 - erlotinib, gefitinib cetuximab and

trastuzumab; and mammalian target of rapamycin - temsirolimus, everolimus, and ridaforolimus [6–16]. The most active is bevacizumab, an monoclonal antibody that inhibits VEGF-A which demonstrated a 13.5% response rate with 40.4% of patients PFS at 6 months [17]. Thus, further development of therapies that not only target the VEGF pathway but other important receptor tyrosine kinases is warranted.

The fibroblast growth factor (FGF) family comprises 18 ligands (FGF1 through FGF10 and FGF16 through FGF23) that signal through four transmembrane receptor tyrosine kinases (FGFR1-R4) and their alternatively spliced isoforms [18]. FGF signaling has been shown to play a crucial role in many physiological and pathological processes including embryogenesis, angiogenesis, and tumorigenesis [19]. Pollock and colleagues first reported activating mutations in FGFR2 and have since reported mutations in 48/466 (10%) endometrioid endometrial cancers [20,21]. This finding has been confirmed by independent groups at a similar frequency [22–26]. Extensive functional analyses have already been performed for many of the mutations, demonstrating they result in constitutive ligand-dependent and ligand-independent receptor activation [20]. EMC cell lines with FGFR2 activating mutations undergo cell cycle arrest and cell death in response to FGFR inhibition with the selective inhibitor PD173074 [27]. Considerable in vitro activity has also been reported for several clinically relevant anti-FGFR compounds [28–30]. Thus, FGFR appears to be a viable therapeutic target for patients with endometrial carcinoma.

Brivanib, an oral medication, is a dual tyrosine kinase inhibitor of VEGFR and FGFR signaling. Brivanib has been evaluated in multiple tumor types with promising antitumor activity [31,32]. A phase II trial of single-agent brivanib was conducted in patients with recurrent or persistent EMC. The primary objective was to evaluate efficacy in terms of both the probability of surviving progression free for at least six months (PFS at six months) and clinical response. Predictive and prognostic biomarker discovery is also incorporated in this trial.

PATIENTS and METHODS

Patient Selection

To be eligible the following criteria were met: histologic confirmation of the primary tumor by central pathology review by the Gynecologic Oncology Group (GOG) Pathology Committee; GOG performance status of 0–2; measurable disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) [33]; one to two prior cytotoxic regimens; chemotherapy was discontinued at least three weeks before registration (hormonal therapy at least one week); recovery from recent surgery, radiotherapy, or chemotherapy; no evidence of active infection requiring antibiotics. Patients must also have had adequate hematologic counts (absolute neutrophil count $\geq 1,000/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$), chemistries (hyponatremia (sodium >129), potassium >3.4 mmol/L), serum creatinine $\leq 1.5 \times$ the institutional upper limit of normal [ULN] and urine protein $<3+$ or <3.5 g/24 hours, serum bilirubin $\leq 1.5 \times$ ULN and AST and alkaline phosphatase $\leq 2.5 \times$ ULN, albumin ≥ 2.5 g/dl), and coagulation profiles (prothrombin time such that international normalized ratio ≤ 1.5 , anticoagulation with low molecular weight heparins were allowed); left ventricular ejection fraction $\geq 50\%$ and QTc on ECG <450 msec; negative pregnancy test before study entry and

agreement to practice an effective form of contraception in patients of childbearing potential. All patients signed approved informed consent in accordance with federal, state, and local requirements and an authorization permitting release of personal health information. Both central and local institutional review board approval were obtained.

Patients were ineligible if they met any of the following criteria: prior use of brivanib or anti-VEGF, anti-FGFR or anti-PDGFR (platelet-derived growth factor receptor) therapy; prior treatment with any noncytotoxic therapy (other than hormonal therapy); other malignancies (except non-melanomatous skin cancer) evident within three years or prior cancer treatment that contradicts eligibility; on required chronic anti-platelet therapy (aspirin >300 mg/day or clopidogrel greater than or equal to 75 mg/day); on therapeutic warfarin anticoagulation; gastrointestinal bleeding or any other hemorrhage/bleeding event (CTCAE Grade 3) within 30 days prior to study entry; history of poor wound healing, non-healing ulcers or bone fractures within the last three months; known brain metastasis; clinically significant cardiovascular disease (myocardial infarction or uncontrolled angina within 12 months, Class III–IV New York Heart Association congestive heart failure), arrhythmias requiring anti-arrhythmic therapy other than beta-blockers or digoxin, valvular heart disease (>CTCAE grade 2); history of stroke, TIA, or other CNS ischemic event; inability to swallow tablets or untreated malabsorption syndrome and a serious uncontrolled medical disorder or active infection (active/known HIV, Hepatitis B, or Hepatitis C, hyponatremia, hypokalemia).

Treatment

Enrolled patients were to receive brivanib 800 mg orally daily (28 day cycle) with dose modification to 600 or 400 mg daily for toxicity. Treatment was planned until disease progression or adverse events prohibited further therapy. Toxicity was monitored with history, physical examination, and laboratory assessment before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Brivanib was held for grade 3 non hematologic toxicity for a maximum of 30 days to allow recovery to grade 1. Brivanib was discontinued for cardiac ischemia or infarction; evidence of cardiac valve dysfunction >CTCAE Grade 2; LVEF decrease by >10% from baseline-echocardiogram and LVEF <45%; QTc >500 milliseconds on two ECGs performed during the same visit and in the absence of possible causes other than protocol therapy; torsade de pointes or sustained ventricular tachycardia; hemorrhage >CTCAE Grade 3; gastrointestinal perforation; arterial thromboembolic events; venous thromboembolic events CTCAE Grade 4; seizures/convulsions thought to be possibly, probably or definitely related to study drug or hyponatremia; Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES) or similar leukoencephalopathy syndrome. Specific guidelines were implemented for modifying the treatment regimen in the event of liver enzyme elevation, bilirubin elevation, hyponatremia, hypertension, and hypothyroidism.

Evaluation Criteria

Activity of brivanib was assessed according to RECIST criteria before each cycle by computed tomography or magnetic resonance imaging at baseline, every other cycle for the first six months, and every three months thereafter.

Translational Research

For each patient, slides from either the primary, recurrent or metastatic tumor were available and plasma was collected prior to cycle 1 (baseline), cycle 2 and cycle 3. Translational studies included sequencing of FGFR2, and immunohistochemistry of FGFR1, FGFR2, FGF1, FGF2, ER, PR-A, and PR-B. In addition, to explore if circulating biomarkers of angiogenesis were predictive of patient outcome, multiple anti-angiogenesis biomarkers in pre- and post-treatment serum samples were measured in duplicate using the Bio-Plex Pro Human Angiogenesis 9-Plex Kit (Bio-Rad Laboratories). The primary clinical/translational results are highlighted in this report and a detailed report of methods and analyses of these endpoints will be reported elsewhere.

Statistical Analysis

The primary endpoints used to evaluate the efficacy of brivanib were tumor response and PFS at six months. A two-stage design with co-primary endpoints was employed in the trial, which used the “minimum C method” as provided in Sill et al. [24] The null hypothesis (H_0) assumed a probability of response and PFS at six months equal to 10% and 15%, respectively, which was derived from a historical control. See Table 1 of Aghajanian et al. for details [17]. Twenty percent increases (≥ 0.20) in either proportion were deemed clinically significant. With 26 patients entered at the first stage, the design required more than three patients with responses or more than five who were PFS at six months before proceeding to the second stage. With a cumulative sample size of 43, the design required at least nine patients with responses or 11 patients PFS at six months before declaring the regimen worthy of further study. The study had 60–68% probability of early termination under H_0 , a 6.6% level of significance, and about 90% power. Secondary endpoints included PFS and OS. Time at risk was determined from the date of protocol entry. Treatment related toxicities were characterized by their frequency and severity according to organ or organ system affected.

Exploratory analyses of biomarkers were conducted to assess pre-treatment associations between biomarkers, patient demographics, and clinical outcome. Translational research yielded hypothesis generating questions when “p-values” were 5% or less; these were deemed suggestive and worthy of follow-up in future studies. Associations with $0.05 < p\text{-value} < 0.10$ were called “potential trends.” To screen for potential effects on PFS and OS, biomarker variables were often dichotomized at their median values for Cox modeling [39] or in log-rank tests [40]. Hazard ratios (HR) were reported for high to low levels of biomarkers. Exact χ^2 tests were used to assess associations with strictly categorical variables [34].

RESULTS

From July 2009 to January 2011, GOG member institutions enrolled 45 patients onto this trial. One patient was deemed ineligible because a required test was not done and another had the wrong primary cancer; the remaining 43 patients were assessable for toxicity and efficacy. Patient characteristics are listed in Table 1. A total of 191 cycles were administered with a median of two cycles (range, 1–24 cycles). Fifteen patients (34.9%) received 4 cycles.

Activity

The clinical activity of brivanib was determined for the 43 eligible patients (Table 2). Eight patients (18.6%; 90% CI 9.6–31.1%) experienced clinical responses (one complete response (CR) and seven partial responses (PRs); median response duration, 6.3 months), and 13 patients (30.2%; 90% CI 18.9–43.7%) were PFS at six months. Median PFS and OS were 3.3 (90% CI 2.0 – 3.9) and 10.7 (90% CI 9.2 – 18.1) months, respectively (Figure 1). One of the 13 patients PFS at six months went off study therapy due to hypertensive crisis and went onto subsequent therapy 2.3 months after study entry. Deeming this patient a treatment failure, the estimated proportion PFS at six months is 27.9% (90% CI 17.0 – 41.3%). There was no suggested association between cell type and patient response or PFS at six months (Table 3).

Adverse Events

As shown in Table 4, safety of brivanib in all 43 patients was analyzed descriptively. No GI perforations but one rectal fistula were reported. One grade 5 event was reported. It did not have a specific CTC adverse event term but was listed as a multi-organ failure. The attribution to the treatment was listed as possible. Additionally, nine patients had grade 3 hypertension. One of these patients had grade 4 confusion and was removed from study secondary to posterior reversible encephalopathy syndrome.

Translational Endpoints

Of the 32 patients for whom adequate tumor DNA was available for analysis, 3/32 (10%) carried activating somatic FGFR2 mutations (2x C383R; 1xN550K+R679S). Mutations were found in 2/16 endometrioid and 1/7 mixed histology tumors for a frequency of 13% (3/23) in these subtypes. From the primary tumors, there was a suggested association between ER expression with OS and cell type. There was a no trend indicated for improved PFS. Plasma collagen levels were not associated with PFS or OS. When modeled separately, none of the angiogenic markers were suggested as being associated with PFS and OS, however, a permutation test (with 10,000 simulations) using a Cox model indicated a potential trend for the factors angiopoietin-2 (Ang-2) and VEGF when modeled jointly. This analysis indicates that patients with higher levels of Ang-2 tend to have a lower risk of progressing (HR=0.28) and patients with higher levels of VEGF tend to have a higher risk of progressing (HR=3.1) (Supplemental Table 1). Patients with high levels of VEGF tended to have high levels of Ang-2, which may have masked these trends when the biomarkers were modeled individually. These results did not translate into OS as strongly but had similar

tendencies (Supplemental Table 2). Ang-2 had an estimated HR=0.52, and VEGF had an estimated HR=1.8. Sample sizes did not permit construction of reliable confidence intervals.

DISCUSSION

While early-stage endometrial cancer is often successfully treated with surgical intervention, treatment of advanced-stage endometrial carcinoma or recurrent disease can be difficult, and the prognosis is poor. The GOG has established levels of activities for targeted therapies in these patients based on historical controls to determine if an agent is of significant interest for further development [23]. Based on this assessment brivanib is worthy of further investigation with 30.2% of patients PFS at six months. Eight patients (18.6%) experienced a clinical response in this study of unselected recurrent or persistent endometrial cancer patients with one or two prior cytotoxic chemotherapy regimens with 56% receiving prior radiation therapy.

Patients receiving brivanib with endometrioid (6 of 19; 31.5%) or mixed epithelial subtypes (4 of 8; 50%) appeared to have the best PFS at six months compared to those with pure serous carcinoma (1 of 10; 10%). Interestingly, the one patient with a complete response and three of six patients with a partial response had serous histology. This variation in response may be different than that achieved with bevacizumab, where responses were seen across all histologic subtypes and the percentage of patients alive and progression-free at six months was similar for serous and endometrioid histologies [17]. The association between ER and OS in this study likely reflects the correlation with ER and cell type, where endometrioid histology has been shown in larger cohorts to be associated with a more favorable prognosis. In addition, ER, VEGFR and FGFR cross talk at this level of signaling, and it is possible that tumors with high ER depend upon downstream growth factor activity through VEGFR and FGFR for proliferation. In such cases, brivanib therapy may be beneficial.

Bevacizumab has shown the most significant activity of the targeted therapies tested to date with a 13.5% response rate and 40.4% of patients progression-free for at least six months [17]. The activity of brivanib is comparable with an 18% response rate and 30.2% of patients progression free at six months. Although brivanib was associated with some increased patient toxicities, it has the advantage of being an oral therapy and thus should be further developed for patients with endometrial carcinoma.

Attempts to identify molecular predictors of response for bevacizumab and other VEGF targeted compounds have been largely unsuccessful across multiple tumor types [35] pointing towards the complex interplay of the many molecules regulating angiogenesis within the tumor, the surrounding stroma and in circulation. When we jointly modeled circulating expression levels of VEGF and Ang-2, patients with higher levels of Ang-2 tended to have a lower risk of progressing while patients with higher levels of VEGF were associated with a higher risk of progressing. This is consistent with an immunohistochemical study of breast cancer patients, which found that Ang-2 was not prognostically significant when modeled; however, the combination of high Ang-2 and high VEGF was predictive of significantly worse PFS than other combinations of VEGF and Ang-2 [36]. The interactions between these biomarkers can be explained by the fact that, at low levels of VEGF, Ang-2 is

anti-angiogenic and can induce endothelial cell death, but at high levels of VEGF, Ang-2 is pro-angiogenic and supports development of blood vessels [37]. Thus, Ang-2 is pro-angiogenic only when VEGF levels are also high. Our result that high Ang-2 levels are associated with longer PFS when accounting for VEGF levels could be an artifact due to low patient numbers or could point to Ang-2 having different roles when associated with different VEGF levels.

Based on the trend identified when VEGF and Ang-2 were modeled together, we propose that these biomarkers should be evaluated in larger endometrial cancer patient cohorts that would also allow a comparison of the predictive value of various combinations of low and high VEGF and Ang-2. Further studies of Ang-2 and VEGF in endometrial cancer are warranted based on the elevation of these factors in patients with diabetes mellitus, a known factor for increased risk of endometrial cancer development [38].

Brivanib is predicted to be a modest FGFR2 inhibitor (IC_{50} : FGFR2 125 nM). As such, we were interested to correlate clinical response with the presence of somatic FGFR2 mutations. FGFR2 activating mutations were identified in 3/23 (13%) tumors presenting with an endometrioid or mixed histology, consistent with previous studies. PFS for these three patients was 2.2, 1.84, and 26 months, however, the patient with the longest PFS was the patient that withdrew from therapy after two months due to toxicity. Subsequent in vitro studies have revealed that brivanib has relatively weak anti-FGFR activity in vitro and in vivo compared to other multi-kinase inhibitors [28] and more specific FGFR inhibitors (unpublished data, Pollock laboratory). Therefore the lack of efficacy of brivanib in these three patients should not be construed as evidence that FGFR2 is not a viable therapeutic target. Results from the ongoing trial testing dovitinib in advanced or metastatic endometrial cancer patients with and without FGFR2 mutations may shed light on this question. However, significant clinical responses may require more potent and more specific FGFR inhibitors. Given the efficacy of anti-angiogenic agents in endometrial cancer, it will be interesting to see whether prolonged clinical responses in FGFR2 mutant patients are seen with more specific inhibitors or those with additional angiogenic activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Wright JD, Fiorelli J, Schiff PB, Burke WM, Kansler AL, Cohen CJ, et al. Racial disparities for uterine corpus tumors: changes in clinical characteristics and treatment over time. *Cancer*. 2009; 115:1276–1285. [PubMed: 19204905]
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014; 64:9–29. [PubMed: 24399786]
3. Miller, DS. Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF Versus Carboplatin/Paclitaxel in Patients with Stage III and IV or Recurrent Endometrial Cancer. *Gynecol Oncol*; Abstracts of the 43rd Annual Meeting of the Society of Gynecologic Oncology; March 24–27, 2012; Austin, Texas, USA. 2012. p. S2-188.
4. Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004; 92:10–14. [PubMed: 14751131]
5. Whitney CW, Brunetto VL, Zaino RJ, Lentz SS, Sorosky J, Armstrong DK, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004; 92:4–9. [PubMed: 14751130]
6. Correa R, Mackay H, Hirte H, et al. A phase II study of sunitinib in recurrent or metastatic endometrial carcinoma: A trial of the Princess Margaret Hospital, The University of Chicago, and California Cancer Phase II Consortia. *J Clin Oncol*. 2010; 28(suppl):399s.
7. Nimeiri HS, Oza AM, Morgan RJ, Huo D, Elit L, Knost JA, 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; 117:37–40. [PubMed: 20117828]
8. McMeekin DS, Sill MW, Benbrook D, Darcy KM, Stearns-Kurosawa DJ, Eaton L, 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; 105:508–516. [PubMed: 17306350]
9. Oza AM, Eisenhauer EA, Elit L, Cutz JC, Sakurada A, Tsao MS, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. *J Clin Oncol*. 2008; 26:4319–4325. [PubMed: 18591547]
10. Albitar L, Carter MB, Davies S, Leslie KK. Consequences of the loss of p53, RB1, and PTEN: relationship to gefitinib resistance in endometrial cancer. *Gynecol Oncol*. 2007; 106:94–104. [PubMed: 17490733]
11. Leslie KK, Sill MW, Fischer E, Darcy KM, Mannel RS, Tewari KS, et al. A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013; 129:486–494. [PubMed: 23438670]
12. Slomovitz C, Miller D, Lu K, et al. Phase II study of cetuximab (Erbix) in patients with progressive or recurrent endometrial cancer. *Gynecol Oncol*. 116:S1–S198.
13. Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM, et al. Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2010; 116:15–20. [PubMed: 19840887]
14. Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J, Provencher DM, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. *J Clin Oncol*. 2011; 29:3278–3285. [PubMed: 21788564]
15. Slomovitz BM, Lu KH, Johnston T, Coleman RL, Munsell M, Broaddus RR, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. *Cancer*. 2010; 116:5415–5419. [PubMed: 20681032]
16. Colombo N, McMeekin DS, Schwartz PE, Sessa C, Gehrig PA, Holloway R, et al. Ridaforolimus as a single agent in advanced endometrial cancer: results of a single-arm, phase 2 trial. *Br J Cancer*. 2013; 108:1021–1026. [PubMed: 23403817]
17. Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2011; 29:2259–2265. [PubMed: 21537039]

18. Ornitz DM, Itoh N. Fibroblast growth factors. *Genome Biol.* 2001; 2:REVIEWS3005. [PubMed: 11276432]
19. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer.* 2010; 10:116–129. [PubMed: 20094046]
20. 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; 26:7158–7162. [PubMed: 17525745]
21. Byron SA, Gartside M, Powell MA, Wellens CL, Gao F, Mutch DG, et al. FGFR2 Point Mutations in 466 Endometrioid Endometrial Tumors: Relationship with MSI, KRAS, PIK3CA, CTNNB1 Mutations and Clinicopathological Features. *PLoS One.* 2012; 7:e30801. [PubMed: 22383975]
22. Dutt A, Salvesen HB, Chen TH, Ramos AH, Onofrio RC, Hatton C, et al. Drug-sensitive FGFR2 mutations in endometrial carcinoma. *Proc Natl Acad Sci U S A.* 2008; 105:8713–8717. [PubMed: 18552176]
23. Gatus S, Velasco A, Azueta A, Santacana M, Pallares J, Valls J, et al. FGFR2 alterations in endometrial carcinoma. *Mod Pathol.* 2011; 24:1500–1510. [PubMed: 21725289]
24. Cheung LW, Hennessy BT, Li J, Yu S, Myers AP, Djordjevic B, et al. High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability. *Cancer Discov.* 2011; 1:170–185. [PubMed: 21984976]
25. Krakstad C, Birkeland E, Seidel D, Kusonmano K, Petersen K, Mios S, 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:e52795. [PubMed: 23300780]
26. Beadling C, Heinrich MC, Warrick A, Forbes EM, Nelson D, Justusson E, et al. Multiplex mutation screening by mass spectrometry evaluation of 820 cases from a personalized cancer medicine registry. *J Mol Diagn.* 2011; 13:504–513. [PubMed: 21726664]
27. Byron SA, Gartside MG, Wellens CL, Mallon MA, Keenan JB, Powell MA, et al. Inhibition of activated fibroblast growth factor receptor 2 in endometrial cancer cells induces cell death despite PTEN abrogation. *Cancer Res.* 2008; 68:6902–6907. [PubMed: 18757403]
28. Gozgit JM, Wong MJ, Moran L, Wardwell S, Mohemmad QK, Narasimhan NI, et al. Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models. *Mol Cancer Ther.* 2012; 11:690–699. [PubMed: 22238366]
29. Guagnano V, Kauffmann A, Wohrle S, Wohrle S, Stamm C, Ito M, et al. FGFR genetic alterations predict for sensitivity to NVP-BGJ398, a selective pan-FGFR inhibitor. *Cancer Discov.* 2012; 2:1118–1133. [PubMed: 23002168]
30. Gavine PR, Mooney L, Kilgour E, et al. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. *Cancer Res.* 2012; 72:2045–2056. [PubMed: 22369928]
31. Finn RS, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, et al. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res.* 2012; 18:2090–2098. [PubMed: 22238246]
32. Park JW, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, et al. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res.* 2011; 17:1973–1983. [PubMed: 21349999]
33. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205–216. [PubMed: 10655437]
34. Mehta CR, Patel NR. A Network Algorithm for Performing Fisher Exact Test in R X C Contingency-Tables. *Journal of the American Statistical Association.* 1983; 78:427–434.
35. Gerger A, LaBonte M, Lenz HJ. Molecular predictors of response to antiangiogenesis therapies. *Cancer J.* 2011; 17:134–141. [PubMed: 21427557]
36. Tsutsui S, Inoue H, Yasuda K, Suzuki K, Takeuchi H, Nishizaki T, et al. Angiopoietin 2 expression in invasive ductal carcinoma of the breast: its relationship to the VEGF expression and microvessel density. *Breast Cancer Res Treat.* 2006; 98:261–266. [PubMed: 16538528]

37. Lobov IB, Brooks PC, Lang RA. Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and endothelial cell survival in vivo. *Proc Natl Acad Sci U S A*. 2002; 99:11205–11210. [PubMed: 12163646]
38. Lim HS, Lip GY, Blann AD. Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. *Atherosclerosis*. 2005; 180:113–118. [PubMed: 15823283]
39. Cox DR. Regression models and life tables. *Journal of the Royal Statistical Society*. 1972; 34:187–220. Series B.
40. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep*. 1966; 50:163–170. [PubMed: 5910392]

Progression-Free Survival and Survival

Figure 1.

Progression-free and overall survival for the 43 evaluable patients

Progression-free survival (PFS) and overall survival (OA) for patients treated with brivanib.

The median PFS was 3.3 months (90% CI 2.0 – 3.9 months). The median OS was 10.7 months (90% CI 9.2 – 18.1 months).

Table 1

Patient and cancer characteristics

Characteristic	Category	No.	(%)
Age	40–49	3	(7.0)
	50–59	12	27.9
	60–69	15	34.9
	70–79	11	25.6
	80–89	2	4.7
Race	African American	4	9.3
	White	39	90.7
Performance Status	0	28	65.1
	1	12	27.9
	2	3	7.0
Cell Type	Clear Cell Carcinoma	5	11.6
	Endometrioid Adenocarcinoma	19	44.2
	Mixed Epithelial Carcinoma	8	18.6
	Undifferentiated Carcinoma	1	2.3
	Serous Adenocarcinoma	10	23.3
Cell Type/Grade	Endometrioid, grade 1	7	16.3
	Endometrioid, grade 2	4	9.3
	Endometrioid, grade 3	8	18.6
	Serous	10	23.3
	Clear Cell	5	11.6
	Mixed Epithelial	8	18.6
	Undifferentiated	1	2.3
Prior Chemotherapy	1 Prior Regimen	26	60.5
	2 Prior Regimens	17	39.5
Prior Radiation	No	19	44.2
	Yes	24	55.8
Prior Surgery	No	3	7.0
	Yes	40	93.0

Table 2

Clinical Activity of brivanib

Characteristic	Category	No.	% of
Response ^I	Complete response	1	2.3
	Partial response	7	16.3
	Stable disease	12	27.9
	Increase disease	15	34.9
	Indeterminate	8	18.6
PFS > 6 Months ^I	No	30	69.8
	Yes	13	30.2
PFS to Next Rx > 6 Months	No	31	72.1
	Yes	12	27.9
Cycles of Treatment	1	6	14.0
	2	18	41.9
	3	4	9.3
	4+	15	34.9

^I Six patients had both response and progression free survival (PFS) at 6 months (OR=12; 90% CI 2.0 – 90.9). The one patient who was PFS at 6 months but began another therapy at after 2.3 months had a best response of stable disease. Rx=anti-cancer therapy.

Table 3

Relationship of histologic sub-type and progression-free survival (PFS)

	PFS>6Months		
	No	Yes	Total
Clear Cell Carcinoma	4	1	5
Endometrioid Adenocarcinoma	13	6	19
Mixed Epithelial Carcinoma	4	4	8
Undifferentiated Carcinoma	0	1	1
Serous Adenocarcinoma	9	1	10
Total	30	13	43

Table 4

Adverse Events (CTCAE) by type and grade for the 43 evaluable patients

AE Category	0	1	2	3	4	5
Leukopenia	29	10	3	1	0	0
Thrombocytopenia	33	8	2	0	0	0
Neutropenia	39	1	3	0	0	0
Anemia	25	11	6	1	0	0
Other Hematologic	40	1	2	0	0	0
Allergy/Immunology	42	1	0	0	0	0
Cardiac	26	4	4	9	0	0
Coagulation	39	0	0	4	0	0
Constitutional	14	12	15	2	0	0
Dermatologic	31	8	3	1	0	0
Endocrine	39	3	1	0	0	0
Nausea	19	17	2	5	0	0
Vomiting	32	6	2	3	0	0
Gastrointestinal	11	15	10	7	0	0
Hemorrhage	42	1	0	0	0	0
Hepatobiliary	42	0	1	0	0	0
Infection	42	0	1	0	0	0
Lymphatics	41	0	2	0	0	0
Metabolic	10	16	11	6	0	0
Musculoskeletal	40	0	2	1	0	0
Neurosensory	37	6	0	0	0	0
Other Neurological	31	7	1	3	1	0
Ocular/Visual	42	1	0	0	0	0
Pain	19	16	5	3	0	0
Pulmonary	34	5	4	0	0	0
Vascular	42	0	0	1	0	0
Death, Not CTC coded	42	0	0	0	0	1