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Permalink

Journal

ISSN

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Chan, John K
Deng, Wei
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et al.

Publication Date

DOI

Copyright Information

Peer reviewed

CrossMark
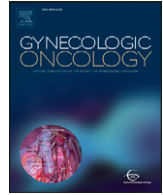
A phase II evaluation of brivanib in the treatment of persistent or recurrent carcinoma of the cervix: An NRG Oncology/Gynecologic Oncology Group study ☆

John K. Chan [a,*], Wei Deng [b], Robert V. Higgins [c], Krishnansu S. Tewari [d], Albert J. Bonebrake [e], Michael Hicks [f], Stephanie Gaillard [g], Pedro T. Ramirez [h], Weldon Chafe [i], Bradley J. Monk [j], Carol Aghajanian [k]

[a] Division of Gynecological Oncology, California Pacific-Palo Alto Medical Foundation, Sutter Cancer Research Institute, San Francisco, CA 94115, United States
[b] NRG Oncology/Gynecologic Oncology Group Statistics & Data Center, Roswell Park Cancer Institute, Buffalo, NY 14263, United States
[c] Division of Gynecological Oncology, Levine Cancer Institute, Charlotte, NC 28203, United States
[d] Division of Gynecological Oncology, University of California, Irvine Medical Center, Orange, CA 92868, United States
[e] Division of Gynecological Oncology, Cancer Research for the Ozarks-Cox Health, Springfield, MO 65807, United States
[f] Division of Gynecological Oncology, Michigan Cancer Research Consortium, Pontiac, MI 48341, United States
[g] Division of Medical Oncology, Duke University Medical Center, Durham, NC 27710, United States
[h] Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States
[i] Division of Gynecological Oncology, Virginia Commonwealth University, Richmond, VA 23298, United States
[j] Division of Gynecological Oncology, Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine at St. Joseph's Hospital, Phoenix, AZ 85016, United States
[k] Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, United States

HIGHLIGHTS

- In this phase II trial, brivanib was well tolerated and had sufficient activity.
- Of 28 patients, 7% had partial response and 43% had stable disease
- Common grade 3 adverse events were hypertension, anemia, hyponatremia, and nausea.

ARTICLE INFO

ABSTRACT

Background. Brivanib is an oral, tyrosine kinase inhibitor against vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor (FGFR). We studied its efficacy and tolerability in persistent or recurrent cervical cancer patients.

Methods. Eligible patients had at least one prior cytotoxic regimen for recurrence and with measurable disease. Brivanib 800 mg was administered orally every day (1 cycle = 28 days) until disease progression or prohibitive toxicity. Primary endpoints were progression-free survival (PFS) >6 months and objective tumor response.

Results. Of 28 eligible and evaluable women enrolled, 11 (39%) had primary surgery and 25 (89%) had prior radiation. Eighteen (64%) received one prior cytotoxic treatment and 10 (36%) had 2 prior regimens. Twelve (43%) had >2 cycles of brivanib with 4 (14%) receiving >10 cycles (range: 1–20). Seven (25%) patients had PFS >6 months (90% CI: 7.3–33.9%). Two (7%) (90% CI: 1.3–20.8%) patients had partial tumor response with duration of 8 and 22 months and 12 (43%) had stable disease. The median PFS was 3.2 months (90% CI: 2.1–4.4). The median overall survival was 7.9 months (90% CI: 6.1–11.7). More common grade 3 adverse events were hypertension, anemia, hyponatremia, hyperglycemia, elevated liver enzymes, nausea, headache, and colon hemorrhage. Grade 4 adverse events included sepsis and hypertension.

Conclusions. Based on early results of this phase II trial, brivanib was well tolerated and demonstrated sufficient activity after first stage but trial was stopped due to lack of drug availability.

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1. Introduction

Cervical carcinoma is the leading cause of cancer-related death in women worldwide. Over 500,000 new cases are diagnosed globally with 250,000 deaths per year [1]. In the United States, 12,990 new cases of cervical cancer were diagnosed and 4,120 women died from this cancer in 2016 [2]. Patients with metastatic, persistent, or recurrent cervical cancers have limited treatment choices and poor prognosis [3]. Novel treatment strategies are needed.

Angiogenic growth factors and their receptors have been identified as important regulators of the growth of cervical and other cancers [4–6]. The incorporation of bevacizumab, a humanized vascular endothelial growth factor (VEGF) neutralizing monoclonal antibody combined with chemotherapy improved the survival of advanced cervical cancer patients [7]. Fibroblast growth factor receptor (FGFR) is another significant regulator of angiogenesis and tumorigenesis that induces endothelial cell proliferation, migration, and differentiation [8].

Brivanib is an orally administered, highly potent, selective inhibitor of VEGFR-2, FGFR-1, and FGFR-2 [9–11]. In a study of metastatic, chemotherapy-refractory colorectal cancer patients, investigators showed that brivanib improved the progression-free survival (PFS) and objective response but not overall survival (OS) [12]. In another phase III clinical trial, brivanib did not improve the OS of hepatocellular carcinoma patients [13]. In gynecologic cancer, the NRG/Gynecologic Oncology Group (GOG) investigators conducted a phase II trial in recurrent or persistent endometrial cancer and found that brivanib was associated with a 30% PFS at 6 months [14]. FGFR expression is up-regulated in cervical neoplasias. In preclinical studies, brivanib delayed the progression of cervical intraepithelial neoplasia grade 2/3 to cervical carcinoma, and inhibited tumor growth in the HPV6/E2 cervical carcinoma mouse model [15].

Given the activity of brivanib in uterine and other cancers, we performed a phase II trial in recurrent or persistent cervical cancer patients to evaluate the efficacy and toxicity of this novel agent.

2. Patients and methods

2.1. Patient selection

We enrolled 31 patients, 1 was deemed ineligible and 2 did not undergo treatment. 28 patients were eligible and treated with follow-up. Patients were eligible if they had persistent or recurrent squamous cell, adenosquamous, adenocarcinoma or non-squamous cell cervical carcinoma with documented disease progression. Histologic confirmation of the original primary tumor is required via the pathology report. All patients must have measurable disease as defined by modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [16,17]. All patients had a GOG performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about >50% of waking hours).

Patients must have had 1 prior systemic chemotherapeutic regimen for management of advanced, metastatic, or recurrent disease. Chemotherapy administered concurrent with primary radiation (e.g. weekly cisplatin) was not counted as a systemic chemotherapy regimen. They were allowed but not required to receive 1 additional cytotoxic regimen for management of recurrent or persistent disease. Patients must have not received any non-cytotoxic (biologic or targeted) agents; in particular, prior use of brivanib or anti-VEGF, anti-FGFR or anti-PDGFR (platelet derived growth factor receptor) therapy. Prior to registration, all chemotherapy was discontinued for at least 3 weeks, hormonal therapy for at least 1 week, and radiotherapy for at least 4 weeks. All patients had adequate bone marrow, renal, hepatic, and neurologic function.

2.2. Treatment

Brivanib (BMS 582664IND# 108417) was self-administered orally 800 mg daily (28 day cycle) until disease progression or adverse events prohibited further therapy. Dose was modified to 600 or 400 mg daily for toxicity. All adverse events were defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0). The drug was held for any grade 3 non-hematologic toxicity to allow recovery. Brivanib was discontinued for cardiac ischemia, infarction or dysfunction, hemorrhage grade 3, gastrointestinal perforation, thromboembolic events, seizures/convulsions, reversible posterior leukoencephalopathy syndrome, posterior reversible encephalopathy syndrome or similar leukoencephalopathy syndrome.

2.3. Evaluation criteria

We assessed the activity of brivanib based on RECIST criteria prior to each cycle by computed tomography or magnetic resonance imaging at baseline, every other cycle for the first 6 months, and every 3 months subsequently.

2.4. Study oversight

The NRG Oncology/GOG designed and conducted this study. The study was approved by the research ethics board at each participating center or by a central institutional review board and all patients provided written informed consent. With reviews by the data and safety monitoring committee, the data were collected, held, and analyzed by the statistical group. The study chair vouches for the integrity of the data, analyses reported, and for the fidelity of the trial to the protocol. Representatives from the sponsors (the Cancer Therapy Evaluation Program of the National Cancer Institute and Bristol Myers Squibb) had no role in the design, accrual, management or analysis of the data. The first author, with input from all the coauthors, drafted the manuscript and made decisions regarding the publication.

2.5. Statistical analysis

Tumor response and PFS at 6 months were the primary endpoints. To evaluate these hypotheses in a 2-stage design, a method provided by Sill and Yothers was used to decide whether there were sufficient numbers of patients who were progression-free at 6 months or with objective responses to continue study in a second stage (at the interim analysis) or deem the drug worthy of further investigation [18]. The null hypothesis (H_0) relating to uninteresting levels of activity was determined from an analysis of historical studies in the GOG-0127 queue, whose enrolled patients were expected to behave similarly to those eligible for this study. The null hypothesis jointly specified the probability of a patient experiencing a tumor response to less than or equal to 10% and the probability of a patient surviving progression-free without non-protocol therapy for at least 6 months to less than or equal to 10%. The alternative hypothesis (H_a) is the complement of the parameter space under H_0. An improvement in the probability of response of 15% or an increase in the probability of event free survival (EFS) at 6 months of 20% would be of clinical interest for further investigation (i.e. a 25% probability of response or a 30% probability of EFS at 6 months). Secondary endpoints were PFS and OS. Time at risk was determined from protocol entry date. Treatment related toxicities were characterized by their frequency and severity according to organ system affected. The trial was stopped early due to lack of drug availability.

3. Results

From April 4, 2011 to September 4, 2012, 28 patients were enrolled and evaluable (median age: 46.5 years). Patient characteristics are listed in Table 1. Twenty-three (82%) were White, 3 (11%) Black, 1 (4%) Asian/Pacific Islander, and 1 (4%) Hispanic. Performance status of 0, 1, and 2 comprised of 19 (68%), 8 (29%), and 1 (4%) patient(s), respectively. The majority (68%) had squamous cell histology. Eleven (39%) had primary surgery and 25 (89%) had prior radiation. Eighteen (64%) received one prior cytotoxic treatment and 10 (36%) had 2 prior chemotherapy regimens. Twelve (43%) had >2 cycles of brivanib with 4 receiving >10 cycles (range: 1–20). Sixty-eight percent of patients discontinued study treatment due to disease progression, and 21% of patients discontinued study treatment due to toxicity. More than half of the patients received 2 or fewer cycles of study treatment. Four patients received >10 cycles of study treatment. Two (7%) (90% CI: 1.3%–20.8%) patients had partial tumor response with duration of 8 and 17 months. The patient with the longest response (16.5 months) discontinued the study drug after 18 courses of brivanib due to clinical progression. Twelve (43%) had stable disease. Five (18%) patients had PFS ≥6 months (90% CI: 7.3%–33.9%). The median PFS was 3.2 months (90% CI: 2.1–4.4). The median OS was 8.6 months (90% CI: 6.1–11.7) (Table 2 and Fig. 1). More common grade 3 adverse events at least possibly related to brivanib were hypertension [4], anemia [4], hyponatremia [4], hyperglycemia [2], elevated liver enzymes [2], nausea [3], headache [2] and colon hemorrhage [1]. Grade 4 adverse events included sepsis [1] and hypertension [1]. (Table 3) Despite sufficient efficacy to proceed to stage 2 trial design, the enrollment was stopped due to lack of drug availability.

4. Discussion

Patients with metastatic, recurrent, or persistent cervical cancers have limited treatment choices and poor prognosis. Previous GOG trials of chemotherapy agents showed response rates of <30% and 6 month PFS of <25% in this patient population [19–25]. Thus, options for

Table 1
Patient characteristics.

Characteristic	Category	No. of cases	% of cases
Age (years)	30–39	8	29%
	40–49	9	32%
	50–59	7	25%
	60–69	2	7%
	70–79	2	7%
Race	White	23	82%
	Black/African American	3	11%
	Hispanic	1	4%
	Native Hawaiian/Pacific Islander	1	4%
Performance status	0	19	68%
	1	8	29%
	2	1	4%
Histology	Squamous cell	19	68%
	Adenocarcinoma	8	29%
	Adenosquamous	1	4%
Tumor grade	1	1	4%
	2	15	54%
	3	11	39%
	Undetermined	1	4%
Prior regimens	1 prior regimen	18	64%
	2 prior regimens	10	36%
Prior Radiation	Yes	25	89%
	No	3	11%
Prior surgery	Yes	11	39%
	No	17	61%

Table 2
Clinical response to treatment.

Endpoint		No. of cases	% of cases
PFS > 6 months	Yes	7	25%
	No	21	75%
EFS > 6 months	Yes	5	18%
	No	23	82%
Clinical response	Partial response	2	7%
	Stable disease	12	43%
	Progressive disease	9	32%
	Indeterminate	5	18%

PFS = progression-free survival, EFS = event-free survival.

treatment of recurrent and metastatic disease are limited and novel therapies are warranted.

Biologic agents for the treatment of gynecologic and other cancers have received significant attention. In particular, the use of anti-angiogenic therapies has shown significant promise in early clinical trials [26,27]. Tewari et al. incorporated bevacizumab, a humanized VEGF-neutralizing monoclonal antibody against VEGF in combination with chemotherapy and showed an improvement in OS in advanced and recurrent cervical cancer patients enrolled in a randomized phase III clinical trial [7]. This study led to the first FDA approval of a biologic agent in patients with advanced and recurrent cervical cancer. Today, bevacizumab combined with chemotherapy is used in first-line treatment of recurrent and metastatic disease in the US. In a recent phase II randomized clinical trial from United Kingdom, Symonds and colleagues showed that cediranib, a tyrosine kinase inhibitor of VEGFR1, 2, and 3, combined with paclitaxel and carboplatin in metastatic or recurrent cervical cancer patients improves progression-free survival [28]. However, most of the patients enrolled in these trials were in the front line setting. Thus, there is an unmet need for patients who have not responded or progressed subsequent to front line treatment particularly after anti-vascular therapy plus chemotherapy.

In this current study, brivanib was administered to predominantly patients with second or third recurrences. In fact, 18 (64%) patients received one prior cytotoxic treatment and 10 (36%) had 2 prior chemotherapy regimens for their recurrent disease. In this group of pretreated patients, the typical responses in the second-line setting with chemotherapy are poor. It is encouraging to find that brivanib resulted in a clinical benefit on 50% of patients, 2 (7%) partial responses with duration of 8 and 17 months and 12 (43%) with stable
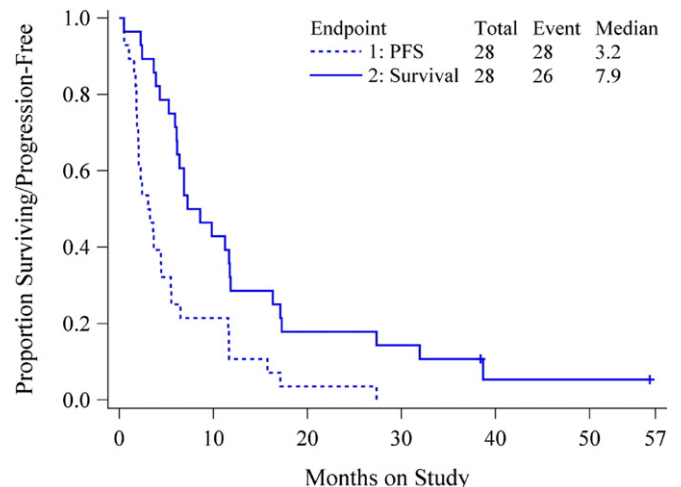

Fig. 1. Kaplan-Meier curves for Progression-Free Survival (PFS) and survival.

Table 3
Adverse events.

	Grade					
	0	1	2	3	4	5
Blood/Lymphatics						
Anemia	5	11	8	4	0	0
Lymphocyte count decreased	23	2	3	0	0	0
Neutrophil count decreased	23	0	5	0	0	0
Platelet count decreased	20	8	0	0	0	0
Cardiovascular						
Hypertension	16	1	6	4	1	0
Left ventricular systolic dysfunction	27	0	0	1	0	0
Pulmonary valve disease	27	0	0	1	0	0
Gastrointestinal						
Nausea	8	9	8	3	0	0
Vomiting	13	8	6	1	0	0
Colonic hemorrhage	27	0	0	1	0	0
Rectal hemorrhage	24	2	1	1	0	0
Nervous system						
Headache	17	4	5	2	0	0
Peripheral sensory neuropathy	20	7	1	0	0	0
Renal/hepatic						
Hematuria	25	1	1	1	0	0
Proteinuria	22	2	4	0	0	0
Alanine aminotransferase increased	21	3	2	2	0	0
Alkaline phosphatase increased	21	5	1	1	0	0
Aspartate aminotransferase increased	20	5	1	2	0	0
Metabolism/nutrition						
Anorexia	13	10	4	1	0	0
Hyperglycemia	20	5	1	2	0	0
Hypokalemia	20	6	1	1	0	0
Hyponatremia	17	7	0	4	0	0
Infectious						
Lung	27	0	0	1	0	0
Abdominal	27	0	0	1	0	0
Urinary tract	23	0	4	1	0	0
Sepsis	27	0	0	0	1	0
Neoplasms/disease progression						
Neoplasms malignant[a]	26	0	0	0	0	2

[a] The 2 deaths were thought unrelated to study treatment and attributable to neoplasms/disease progression.

disease. In another phase II study of advanced and recurrent cervical cancer patients after at least one prior regimen, Monk et al. showed that pazopanib improved PFS and OS, confirming the activity of anti-angiogenesis agents in these patients [29]. On the other hand, it is important to note that all patients enrolled in these two trials excluded those who have been exposed to any non-cytotoxic (biologic or targeted) agents; in particular, prior use of anti-VEGF, anti-FGFR or anti-PDGFR (platelet derived growth factor receptor) therapy. During the initial design and enrollment of this trial, bevacizumab was not FDA approved. Today, most recurrent cervical cancer patients will have been treated with bevacizumab; thus, it remains to be determined if brivanib or pazopanib will have significant clinical benefit in those after anti-vascular therapy.

Fibroblast growth factor (FGF) is significant regulator of angiogenesis and tumorigenesis that induces endothelial cell proliferation, migration and differentiation. FGF signaling regulates tumor growth and vascularization and partly mediates anti-angiogenic escape from VEGF receptor inhibitors [5]. A highly potent, selective inhibitor of VEGF and FGFR, brivanib demonstrated significant activity in early clinical studies in solid tumors [9–11]. In a phase III study of metastatic colorectal cancer patients, brivanib was associated with an improved PFS [12]. However, brivanib did not improve the OS of patients with un-resectable, advanced hepatocellular carcinoma [13]. In gynecologic cancer, the NRG/GOG conducted a phase II trial in recurrent or persistent endometrial cancer and found a 30% PFS at 6 months [14]. In this current report of recurrent and metastatic cervical cancer patients who relapsed on chemotherapy, the PFS ≥6 months at 25% in this heavily pretreated group of patients. These results are particularly encouraging given that over one-third of women progressed after two prior lines of chemotherapy.

Based on prior studies on various chemotherapy regimens in these patients, the response rates range from only 10 to 20% [19–25]. With biologic regimens, the 6 month PFS endpoint has been used as a measure for activity. After a phase III randomized trial, the FDA approved the anti-vascular agent, bevacizumab in combination with chemotherapy for recurrent and metastatic cervical cancer. A prior phase II trial with bevacizumab as a single agent showed a 24% PFS at six months [26]. Brivanib has comparable results with 6 month PFS of 25%. Other biologic agents such as erlotinib [30], cetuximab [27], and temsirolimus [31] have 6 month PFS of 4%, 14%, and 28%, respectively. The activity of oral brivanib was comparable to other biologic agents in recurrent cervical cancer patients. (Table 4) However, it is unclear if anti-VEGF/FGFR is better than anti-VEGF alone in advanced cervical cancer. In phase II trials from the GOG on uterine cancer, the PFS of those who received brivanib compared to bevacizumab appears comparable [14,32].

Similar to other tyrosine kinase inhibitors targeting VEGF, such as sunitinib and sorafenib, we also observed comparable adverse events associated with brivanib including hypertension, hypothyroidism, and proteinuria [33,34]. However, unlike other tyrosine kinase inhibitors, hyponatremia appears to be an adverse event distinctly associated with brivanib. This finding has been reported in other studies on hepatocellular and colorectal cancer patients [35,36]. There were no treatment-related deaths reported during the period of active treatment or within 30 days of last study treatment. Compared to bevacizumab, brivanib has the advantage of being an oral therapy. Given the results of this study, further validation of it clinical activity and toxicity in a phase III trial is warranted.

Although the first stage results demonstrated sufficient efficacy to continue to second stage of accrual, this trial will not proceed to the second stage because of lack of interest by the company to further develop this agent based on randomized clinical trials results in other cancers. Nevertheless, other FGF inhibitors are currently under investigation such as nintedanib and dovitinib. Nintedanib was approved in the European Medicines Agency for advanced lung adenocarcinoma and

Table 4
Single agent biologic agents for recurrent or metastatic cervical cancer – phase II trials.

Biologic	Target	Author, year	Group	# of pts	RR	PFS ≥ 6 months
bevacizumab	VEGF	Monk, 2009 [26]	NRG/GOG	46	11%	24%
erlotinib	EGFR	Schilder, 2009 [30]	NRG/GOG	25	0%	4%
pazopanib	VEGFR, PDGFR, FGFR	Monk, 2010 [29]	GSK	74	9%	–
lapatinib	EGFR, HER2	Monk, 2010 [29]	GSK	78	5%	–
cetuximab	EGFR, HER1	Santin, 2011 [27]	NRG/GOG	35	0%	14%
temsirolimus	mTOR	Tinker, 2013 [31]	NCIC	37	3%	28%
Brivanib	VEGFR, FGFR	Chan, 2016	NRG/GOG	28	7%	25%

RR = response rate, PFS = progression-free survival.
VEGF = Vascular endothelial growth factor, EGFR = Epidermal growth factor receptor, PDGFR = Platelet-derived growth factor receptors, FGFR = Fibroblast growth factor receptor, HER2 = human epidermal growth factor receptor 2, mTOR = mammalian target of rapamycin complex.
GOG = Gynecologic Oncology Group, GSK = GlaxoSmithKline.

approved by the United States FDA for slowing the progression of idiopathic pulmonary fibrosis [37,38]. Other studies have shown that this FGF inhibitor is active in advanced renal cell cancer patients; however, the GOG study found that it lacked sufficient activity in recurrent or persistent endometrial cancer [39,40]. In advanced or recurrent cervical cancer, the European Network of Gynaecological Oncological Trial Groups and Belgium and Luxembourg Gynaecologic Oncology Group is currently comparing carboplatin plus paclitaxel with or without nintedanib. Another FGF inhibitor, dovitinib, was found to be active in progressive renal cell cancer following VEGFR tyrosine kinase inhibitors and mTOR inhibitors [41]. In addition to identifying more specific and effective FGF inhibitors in cervical cancer, novel biomarkers are needed to identify those patients who are more likely to respond to these agents.

Conflicts of interest

Acknowledgment

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