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A Phase II Evaluation of Nintedanib (BIBF-1120) in the Treatment of Recurrent or Persistent Endometrial Cancer: An NRG Oncology/Gynecologic Oncology Group Study

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Abstract

Introduction—Patients presenting with advanced, recurrent, or metastatic endometrial cancer have limited treatment options. On behalf of the Gynecologic Oncology Group, we conducted this phase II trial of nintedanib (BIBF 1120), a potent small molecule triple receptor tyrosine kinase inhibitor of PDGFR α and β , FGFR 1/3, and VEGFR 1-3, in this population.

Objectives—The primary objectives were to estimate event-free survival (EFS) at six months and the proportion of patients who have an objective tumor response. In addition, we sought to determine the nature and degree of toxicity. Secondary objectives were to estimate progression-free and overall survival.

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CONFLICTS OF INTEREST

The co-authors have no conflicts of interest to declare.

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Methods—This was a two-stage, single-arm phase II study. Eligible patients were treated with single-agent nintedanib at a dose of 200 mg twice daily.

Results—Of 37 patients enrolled, 32 were eligible. There were zero complete and three partial responses for an overall response rate of 9.4% (90% 2-sided CI 2.6 ~ 22.5%). Seven patients (21.9%; 90% 2-sided CI 10.7 ~ 37.2%) were EFS at six months, with one patient continuing on study at the time of this writing. Serious toxicity included the following grade 3 events: gastrointestinal toxicity (5), neutropenia (1), edema (1), hypertension (1), and liver function abnormalities (5).

Conclusions—Nintedanib lacked sufficient activity as a single agent to warrant enrollment to second stage. However, preclinical data indicate it may be synergistic with paclitaxel in a population of patients enriched for specific p53 mutations that result in loss of function. Subsequent studies may evaluate this agent in combination with paclitaxel.

Keywords

Endometrial cancer; angiogenesis inhibitor; clinical trial

INTRODUCTION

Endometrial cancer affects over 50,000 women in the United States alone, and is responsible for approximately 8,600 deaths each year [1]. Unfortunately, for women diagnosed with advanced disease, experience a recurrence, or develop metastatic disease, treatment options are limited. While platinum-based regimens are often administered as initial therapy, there are few options for women who experience a subsequent relapse. This highlights the need for new therapies in advanced or recurrent endometrial cancer.

The degree of neovascularization in malignant tissues has been recognized as a prognostic factor for the course of various human cancers, e.g. breast cancer, cancer of the prostate, ovarian cancer, and lung cancer [2]. Thus far, vascular endothelial growth factor (VEGF) has been the most studied factor promoting the “angiogenic switch” in the growing tumor [3]. VEGF is up-regulated in almost all tumors, is an independent prognostic indicator in most types of human cancers, and is correlated with the risk for relapse and metastatic spread as well as with reduced survival [4,5]. Specific to uterine cancers, McMeekin, et al. evaluated thalidomide in refractory endometrial cancer and demonstrated an association between elevated plasma VEGF levels and poor prognosis [4].

Single agent trials of angiogenesis inhibitors have been conducted in this population, and while not resulting in high response rates, notable evidence of disease stabilization has been reported. In one trial, 52 women with recurrent endometrial carcinoma (36% who received two prior lines of therapy) were treated with bevacizumab as a single agent [6]. The overall response rate (ORR) was 13.5 percent with 40 percent without evidence of progression at six months (progression-free survival (PFS) at six months). In a separate trial, Aflibercept (VEGF-Trap) was administered to 44 evaluable patients [7]. Although there were no clinical responses, the PFS at six months was 41%. Unfortunately, excessive toxicity was seen in

this trial, with two deaths attributed to gastrointestinal perforation and arterial rupture, both deemed to be at least possibly related to treatment.

Recent work has also identified mutations in fibroblast growth factor receptor 2 (FGFR2) in 16% of endometrial cancers [8], which further research has shown are mutually exclusive with K-Ras mutations and are seen concomitantly with PTEN mutations. In one phase II trial in this population, the triple angiokinase agent brivanib was evaluated with a 19% response rate and PFS at six months of 30% [9].

Nintedanib is a potent small molecule triple receptor tyrosine kinase inhibitor of PDGFR alpha/beta, FGFR 1/3, and VEGFR 1-3. It is thought to inhibit the signaling cascade that mediates angiogenesis by binding the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain which interferes with the auto-phosphorylation of receptor homodimers, blocking cross-linking from occurring. It has shown good preclinical anti-tumor efficacy at doses of 50–100 mg, and results in a substantial delay of tumor growth in a broad range of tumors. A phase III trial of carboplatin plus paclitaxel with or without nintedanib for the first-line treatment of ovarian cancer (NCT01015118) has completed accrual [10]. As presented at the 2013 European Society of Gynecologic Oncology biennial meeting, the incorporation of nintedanib was associated with a significant improvement in progression free survival (median, 17.3 versus 16.6 months without nintedanib, HR 0.84, 95% CI 0.72–0.98). [11]

Given the activity of nintedanib in multiple solid tumors and promising activity in ovarian cancer, and in light of the activity of other antiangiogenesis agents in endometrial cancer, the Gynecologic Oncology Group (GOG) initiated this single-arm phase II trial for women with previously treated, recurrent or advanced endometrial cancer.

METHODS

Patient selection

The full eligibility of this study (NCT01225887) can be found online at www.clinicaltrials.gov. In general, all patients must have had: a diagnosis of recurrent or persistent endometrial carcinoma, deemed by their clinician to be refractory to curative therapy or established treatments, with histologic confirmation of the original epithelial primary tumor by the GOG Pathology committee; mMeasurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [12]; and GOG Performance Status of 0 to 2. Patients may have had up to two prior chemotherapeutic regimens for treatment of endometrial cancer. However, patients were excluded if they were previously treated with biologic or targeted therapy, including (though not limited to) monoclonal antibodies, cytokines, and small molecule inhibitors of signal transduction, or prior therapy with nintedanib. All patients had to sign an approved informed consent and authorization permitting release of personal health information prior to enrollment. All institutions required approval by their local Institutional Review Board before trial initiation.

TREATMENT

Patients self-administered nintedanib orally at 200 mg (two 100 mg capsules) twice a day for a 28-day cycle. Patients were instructed to swallow the capsules with a full 8 ounce glass of water and with a dose interval of approximately 12 hours. They were also instructed to take their medication at approximately the same time every day, after food intake. Patients were advised to avoid sun exposure or artificial UVA/UVB radiation and to continue these protections for at least two weeks after drug discontinuation. Treatment was planned until disease progression or adverse events precluded continuation of study treatment. Toxicity was monitored regularly by history, physical examination, and laboratory assessment before each cycle. Adverse events were defined and graded according to Common Toxicity Criteria for Adverse Events (version 4.0).

Dose modifications

Subsequent cycles of therapy were held in the presence of neutropenia (ANC <1500 cells/mcl) or thrombocytopenia (<100,000/mcl) for a maximum of two weeks. In addition, treatment was held for any of the following: nausea grade 3 despite maximal supportive care, vomiting grade 2 despite maximal supportive care, diarrhea grade 3 (or grade 2 symptoms persisting for more than seven consecutive days despite maximal supportive care), hepatic function abnormalities (AST and/or ALT grade 2 in conjunction with bilirubin Grade 2; AST and/or ALT Grade 3), or other non-hematologic toxicity of CTCAE grade 3 considered at least possibly drug related. Dose reduction was required for: grade 4 neutropenia persisting for seven or more days, grade 4 thrombocytopenia, and any of the above non-hematologic toxicities upon recovery.

Evaluation criteria

Response and progression were evaluated in using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) [12], which measures changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes. Imaging was required after every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months, then every three months thereafter until disease progression was confirmed. Responses required confirmation four weeks from initial documentation.

Statistics

The primary objective of the study was to evaluate the efficacy of the study agent through the frequency of patients with objective tumor responses and the frequency who survived event-free for at least six months (six-month EFS). The endpoints for EFS were progression, death, or beginning a subsequent therapy. Benefit in terms of either objective tumor response or event free survival were considered worthy of further investigation from phase II studies since they are expected to be useful surrogates for overall survival.

The null hypothesis (Ho) relating to uninteresting levels of activity was determined from an analysis of a historical dataset based on a similar population of patients where the levels of

activity of the study drugs were believed to be inactive to modestly active. The null hypothesis jointly specified the probability of a patient experiencing a tumor response to 10% and the probability of a patient surviving event-free for at least six months to 20%. The alternative hypothesis (H_a) is the complement of the parameter space under H_0 . Clinically significant differences were a 20% increase in the probability of being EFS at six months or a 15% increase in the probability of response.

The null hypothesis was evaluated with a flexible method provided by Sill et al., which is a two-stage design used to limit patient exposure to inactive regimens by utilizing multiple endpoints (EFS at six months, OS, and the initiation of post-progression therapy) as a single composite endpoint [13]. If the observed numbers of patients with responses or six-month EFS were both less than or equal to their respective critical values, then the study would close, and the regimen would be declared clinically uninteresting. Otherwise, with medical judgment indicating, the study would open to the second stage of accrual to further evaluate the regimen. If either the number of patients with responses or who demonstrated six-month EFS exceeded their respective critical values, then the regimen would be considered worthy of further investigation in a phase III trial.

The targeted accrual for the first stage was 32 patients but was allowed to deviate for administrative purposes. If 32 patients were accrued, the critical value for the number of patients with responses was four and the critical value for the number of patients who reached six-month EFS was seven. The cumulative targeted accrual for the second stage would have been 52, but was allowed to deviate. If 52 patients were accrued, the critical value for the number of patients with responses would have been eight and the critical value for the number of patients who reached EFS at six months was 12.

The goal of the design was to limit the expected probabilities of type I and II errors to approximately 10% under the assumed accrual ranges of 28–35 (stage 1) and 48–55 (cumulatively after stage 2). Using the method of Sill et al., the expected type I error at the end of stage two was about 9–10%, depending on the level of association between response and six-month EFS [13]. The expected probability of early termination when the agent is uninteresting was likely between 46% and 57%, depending on the level of association between the two variables. The study has about 90–92% power of detecting a clinically significant effect, depending on the level of association between the primary endpoints.

RESULTS

Patient Characteristics

Between October 2011 and October 2012, 37 patients were enrolled onto this study. Five patients were deemed ineligible because of prior treatment ($n=1$), inadequate pathology ($n=2$), and insufficient eligibility work-up ($n=2$). The remaining 32 patients were assessable for toxicity and for response. Patient characteristics are listed in Table 1. The majority of patients enrolled were 60 years and older (including 13 who were 70 years), Caucasian, and maintained an excellent performance status. Forty percent of these patients had a serous carcinoma; grade 2 or 3 endometrioid carcinoma comprised an additional 43 percent of the study sample.

Adverse Events

The safety of nintedanib is presented in Table 2. There were no grade 4 or 5 toxicities recorded, and no events of perforation were documented. The predominant toxicities were gastrointestinal and included treatment-related hepatic enzyme elevations. Serious toxicity (grade 3) was limited to gastrointestinal toxicity (5), liver function abnormalities (5), diarrhea (3), and isolated events of edema, hypertension, neutropenia, and nausea/vomiting.

Efficacy

Efficacy is summarized in Table 3. Of 32 evaluable patients, three had a confirmed partial response (9.4%) with stable disease in an addition 34%. The EFS and PFS at six months were 21.9%. We identified no significant difference (statistical or clinical) in PFS by cell type; the median PFS for serous carcinomas was 3.15 months (95% CI 1.58–3.84); for endometrioid tumors, it was 3.58 months (95% CI 1.71–5.62).

A total of 138 cycles were administered with a median of two cycles given (range, 1 to 12). Eight patients continued on treatment past six cycles (one patient continued on therapy in error after progressing within four months of study entry). Two patients continued therapy for 12 cycles at the time of this report. Median PFS was 3.3 months and OS was 10.1 months (Figure 1). The point estimate indicated that older patients had a higher hazard of progression on this study, but these results did not reach statistical significance (HR for PFS 1.71, 95% CI 0.82–3.58).

DISCUSSION

Based on the pre-specified rules, nintedanib does not appear to be an active single agent in this population particularly when compared to other agents tested in this population (Table 4). Despite this, there may be further opportunities to investigate this agent in endometrial cancer. Future trials would require the incorporation of viable hypothesis, aimed at characterizing potential biomarkers that might predict who may benefit from treatment. Such efforts have been met with success in other settings within oncology, including the use of tyrosine kinases against bcr/abl for chronic myelogenous leukemia and crizotinib for lung cancers that test positive for the anaplastic lymphoma kinase (ALK) fusion oncogene protein. Unfortunately, patients did not undergo collection of tissue or blood specimens, which might have helped delineate if the presence of an FGFR mutation correlated with response, which was reported in a similar study using the multi-targeted tyrosine kinase inhibitor, brivanib [9].

Based on ongoing clinical trials in ovarian cancer, the other potential utilization of this agent might be to combine it with chemotherapy. This too has a track record of success in oncology, most notably with the use of chemotherapy plus trastuzumab in the treatment of human epidermal growth factor 2 (HER2)-positive breast cancer. Recently, data from Leslie, et al. suggest that there may be a subpopulation that is likely to benefit from this approach [14]. In work performed in serous uterine carcinomas (90% of which have dysregulation of p53), she has shown in preclinical models that nintedanib induces synthetic lethality specifically in p53-null endometrial cancers by restoring taxane sensitivity and inducing

mitotic cell death. In addition, the preliminary results of the phase III trial in advanced ovarian cancer discussed above suggest that the combination of nintedanib plus chemotherapy may be effective. [11]

In conclusion, the lack of single agent activity should not preclude further investigation of this agent in endometrial cancer. Future trials should be hypothesis-driven and aimed at identifying biomarkers that would predict who will benefit from treatment with nintedanib, most likely in combination with chemotherapy.

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RESEARCH HIGHLIGHTS

- Women with advanced endometrial cancer require better treatments.
- Nintedanib had minimal clinical activity in women with endometrial cancer.
- Follow-up trials should evaluate nintedanib with chemotherapy.

Figure 1.
Progression-free and overall survival.

Table 1

Patient Characteristics (n= 32)

Characteristic	Category	n (%)
Age Group	30–39	1 (3.1)
	50–59	4 (12.5)
	60–69	14 (43.8)
	70–79	10 (31.3)
	>=80	3 (9.4)
Ethnicity	Hispanic	1 (3.1)
	Non-Hispanic	26 (81.3)
	Unknown/Unsp.	5 (15.6)
Race	Caucasian	25 (78.1)
	Black/African American	6 (18.8)
	Asian	1 (3.1)
Performance Status	0	17 (53.1)
	1	14 (43.8)
	2	1 (3.1)
Histology	Endometrioid	
	Grade 1	1 (3.1)
	Grade 2	8 (25.0)
	Grade 3	6 (18.8)
	Serous	13 (40.6)
	Clear Cell	2 (6.3)
	Mixed Epithelial	2 (6.3)

Table 2

Adverse events (n= 32)

AE Category	1	2	3	4	5	Percent
Nausea	15	5	1	0	0	65.6
Diarrhea	17	1	3	0	0	65.6
Metabolism/nutrition	10	8	0	0	0	56.3
General and administration site	12	4	1	0	0	53.1
Other Gastrointestinal [^]	8	3	1	0	0	37.5
Anemia	10	2	0	0	0	37.5
ALT Increased	6	4	2	0	0	37.5
AST Increased	6	4	2	0	0	37.5
Vomiting	9	2	1	0	0	37.5
Alkaline phosphatase Increased	9	1	1	0	0	34.4
All nervous system	10	0	0	0	0	31.3
Leukopenia	4	2	0	0	0	18.8
Renal/urinary	5	0	0	0	0	15.6
Vascular disorders	1	2	1	0	0	12.5
Thrombocytopenia	3	0	0	0	0	9.4
Neutropenia	2	0	1	0	0	9.4
Peripheral sensory neuropathy	3	0	0	0	0	9.4
Psychiatric	2	1	0	0	0	9.4
Respiratory/thoracic	3	0	0	0	0	9.4
Skin/subcutaneous	3	0	0	0	0	9.4
Musculoskeletal	2	0	0	0	0	6.3
Bilirubin increased	1	1	0	0	0	6.3
Cardiac	1	0	0	0	0	3.1
Hepatobiliary	0	1	0	0	0	3.1
Reproductive/breast	0	1	0	0	0	3.1

[^] Includes abdominal distention (n=1), abdominal pain (n=7), constipation (n=3), dry mouth (n=2), flatulence (n=2), gastritis (n=1)

Table 3

Efficacy (n= 32)

Characteristic	Category	N	%
Response	Partial response	3	9.4
	Stable disease	11	34.4
	Increase disease	15	46.9
	Indeterminate	3	9.4
PFS > 6 Months	No	25	78.1
	Yes	7	21.9
EFS > 6 Months	No	25	78.1
	Yes	7	21.9
Cycles of Treatment	1	5	15.6
	2	12	37.5
	3	1	3.1
	4	2	6.3
	6	4	12.5
	7+	8	25

Biologic therapies in endometrial cancer evaluated by the Gynecologic Oncology Group

Table 4

Agent	N	ORR (%)	PFS at 6 months (%)	Progression-Free Survival (Median, months)	Overall survival (Median, months)
Thalidomide ⁴	34	12.5	8.3	1.7	6.3
Gefitinib ¹²	26	3.8	15.4	1.8	7.1
Lapatinib ¹³	30	3.3	10	1.8	7.3
Bevacizumab ⁵	52	13.5	40.4	4.2	10.5
Aflibercept ⁶	44	6.8	40.9 ^a	2.9	14.6
Brivanib ⁸	43	18.6	30.2	3.3	10.7
Nintedanib	32	9.4	21.9	3.3 ^b	10.1 ^c

^aThe proportion of patients EFS at 6 months in this study was 23%, which was significantly less than 40.9%. Patients who went off of study therapy for toxicity were often scanned for progression less frequently, which probably produced an artificially high frequency of patients PFS at 6 months. The longer median OS may have resulted in part from selection bias.

^bThe 90% CI for median PFS is 1.9 ~ 3.84 months.

^cThe 90% CI for median OS is 6.0 ~ 14.0 months.