Phase II Trial of Cabozantinib in Recurrent/Metastatic Endometrial Cancer: A Study of the Princess Margaret, Chicago, and California Consortia (NCI9322/PHL86)

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ABSTRACT

Purpose: The relevance of the MET/hepatocyte growth factor pathway in endometrial cancer tumor biology supports the clinical evaluation of cabozantinib in this disease.

Patients and Methods: PHL86/NCI#9322 (NCT01935934) is a single arm study that evaluated cabozantinib (60 mg once daily) in women with endometrial cancer with progression after chemotherapy. Coprimary endpoints were response rate and 12-week progression-free-survival (PFS). Patients with uncommon histology endometrial cancer (eg, carcinosarcoma and clear cell) were enrolled in a parallel exploratory cohort.

Results: A total of 102 patients were accrued. Among 36 endometrioid histology patients, response rate was 14%, 12-week PFS rate was 67%, and median PFS was 4.8 months. In serous cohort of 34 patients, response rate was 12%, 12-week PFS was 56%, and median PFS was 4.0 months. In a separate cohort of 32 patients with uncommon histology endometrial cancer (including carcinosarcoma), response rate was 6% and 12-week PFS was 47%. Six patients were on treatment for >12 months, including two for >30 months. Common cabozantinib-related toxicities (>30% patients) included hypertension, fatigue, diarrhea, nausea, and hand–foot syndrome. Gastrointestinal fistula/perforation occurred in four of 70 (6%) patients with serous/endometrioid cancer and five of 32 (16%) patients in exploratory cohort. We observed increased frequency of responses with somatic *CTNNB1* mutation [four partial responses (PRs) in 10 patients, median PFS 7.6 months] and concurrent *KRAS* and *PTEN/PIK3CA* mutations (three PRs in 12 patients, median PFS 5.9 months).

Conclusions: Cabozantinib has activity in serous and endometrioid histology endometrial cancer. These results support further evaluation in genomically characterized patient cohorts.

Introduction

Endometrial cancer is the most common gynecologic cancer affecting North American women. Approximately 30% of women with endometrial cancer present with advanced disease, and those with recurrence or distant metastases have a poor prognosis, with 5-year survival rates of less than 20% (1). Platinum-based chemotherapy with paclitaxel and/or doxorubicin remains the standard first-line treatment (2–4). Unfortunately, tumor response rates are below 50% and duration of disease control is under a year. Responses to second-line chemotherapy are transient, with median progression-free-survival (PFS) of 3–4 months. Although several novel cytotoxics and targeted agents have been evaluated, none has demonstrated sufficient activity to gain regulatory approval; and treatment options for women with recurrent disease remain limited (5, 6).

The association of high microvessel density and proangiogenic gene expression with aggressive biology and inferior outcome across different histotypes of endometrial cancer provides biologic rationale to target angiogenic pathways across the histologic spectrum of this disease (7–10). Several approaches have been evaluated with mixed results. Modest efficacy has been observed with both bevacizumab and cediranib, with response rates of approximately 13% and 6-month PFS rates of 40% and 29%, respectively (6, 11); while aflibercept, nintedanib, and sunitinib all had insufficient activity in early studies for further development (12–14). A range of mechanisms have been implicated in intrinsic and acquired resistance to VEGF targeting, including activity through various growth factor pathways and epithelial/stromal cross-talk through MET [also known as tyrosine-protein kinase Met or hepatocyte growth factor receptor (HGFR)], Tie2 and RET (9, 10, 15–17). The recognized relevance of growth factor pathways in promoting angiogenesis provides the basis for studying combination strategies simultaneously directed against VEGF and other mitogenic pathways. One such approach, of bevacizumab with temsirolimus, demonstrated

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Prior presentation: Presented at 2017 American Society of Clinical Oncology (ASCO).

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Clin Cancer Res 2020;26:2477–86

doi: 10.1158/1078-0432.CCR-19-2576

Translational Relevance

Although cytotoxic chemotherapy remains the standard treatment for recurrent/progressive endometrial cancer, clinical benefit is short-lived and toxicity significant. Despite the high frequency of genomic aberrations characterizing endometrial cancer, the development of molecularly targeted agents has been challenged by an incomplete understanding of molecular predictors of response. This single-arm study demonstrates an encouraging signal of activity for cabozantinib across different histologic and molecular subtypes of endometrial cancer. The observation of increased frequency of responses in patients with tumors harboring *CTNNB1* mutation or concurrent *KRAS* and *PTEN/PIK3CA* mutations, is hypothesis generating for future studies. The results reported here not only provide support for the further evaluation of cabozantinib in endometrial cancer, but also justify the critical need for endometrial cancer drug studies to be inclusive, enrolling broad, molecularly characterized, patient populations to facilitate insights into the heterogeneity of clinical benefit, and factors predictive of resistance and response.

impressive efficacy but significant toxicity and has not moved forward into further evaluation (18).

Cabozantinib is a multitargeted tyrosine kinase inhibitor with potent activity against MET (HGF receptor), VEGFR2, RET, and AXL. It has already demonstrated antitumor activity in medullary thyroid (19, 20), renal (21–23), and hepatocellular carcinoma (24). NCI9322/PHL86 was developed to explore the efficacy and toxicity of dual targeting of mitogenic and angiogenic signaling using cabozantinib in women who had previously received chemotherapy for advanced endometrial cancer.

Patients and Methods

Study design and participants

NCI9322/PHL86 (NCT01935934) was a nonrandomized, multicenter, trial of cabozantinib in patients with advanced endometrial cancer, with participation of 12 North American centers of the Princess Margaret Cancer Centre (Toronto, Ontario, Canada), California, and Chicago Phase II Consortia. Eligible patients were ≥18 years old, had received one prior line of chemotherapy for metastatic disease, or had recurrence within a year of adjuvant, platinum-based chemotherapy. Patients with endometrioid and serous adenocarcinomas were eligible for accrual to the experimental cohort and uncommon histology types (including carcinosarcoma, clear cell etc.) to a parallel exploratory cohort. Prior hormonal therapy was allowed, as were targeted agents not directed against MET or VEGF/VEGFR; prior bevacizumab treatment was excluded. All patients required histologic diagnosis with available archival samples, measurable disease by RECIST version 1.1., Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and an estimated life expectancy of ≥3 months. Normal organ and marrow function had to be confirmed within 7 days of the first dose of cabozantinib.

Patients on therapeutic anticoagulation with warfarin, heparin, factor Xa inhibitors, or antiplatelet agents were excluded; prophylaxis with low-dose aspirin (≤81 mg/day), warfarin (≤1 mg/day), or heparin was allowed. In May 2016, inclusion criteria were expanded to allow therapeutic anticoagulation with low-molecular-weight heparin.

Other ineligibilities included gastrointestinal (GI) bleeding requiring intervention within prior 6 months, pulmonary hemorrhage within prior 3 months, endotracheal/bronchial tumor, or tumor-invading GI tract or invading/in contact with major blood vessels, and active brain metastases or epidural disease. Conditions with increased risk of GI fistula/perforation (eg, inflammatory bowel disease, mucosal metastases, prior bowel obstruction, fistula/perforation, or intra-abdominal abscess) were also excluded. Those with uncontrolled intercurrent/recent illness, pregnancy, uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg with optimal antihypertensive treatment) and active hepatitis were not eligible.

Previous adequately treated, basal or squamous cell cancer and superficial bladder cancer were allowed, as were other prior cancers, provided patient had received definitive therapy and maintained disease-free status for at least 3 years.

Major or minor surgeries had to be completed within 3 and 1 month of initiation of cabozantinib, respectively, and radiation to thorax, abdomen, or pelvis, prior to 3 months. A wash-out period of 14 days (or five half-lives of active agent) was required for patients previously treated with small-molecule kinase inhibitors or hormonal therapies, 3 weeks for cytotoxic therapy including investigational cytotoxics or biologics, and 6 weeks for nitrosoureas or Mitomycin C. All other investigational agents needed to be discontinued 4 weeks prior.

Study was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines, with protocol being approved by the institutional ethics review board at each study site. All patients provided written informed consent prior to any study-related procedures.

Treatment

Cabozantinib was administered orally, 60 mg daily, on a 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or death. Initial study design included dose escalation to 80 mg after cycle 1 in patients with stable or progressive disease, and grade ≤1 toxicities. At stage I analysis, study was amended to remove dose escalation option due to a lack of tolerability.

Response assessment was per RECIST v1.1 after cycle 1 and 3, subsequently every 8 weeks irrespective of missed or held doses. Patients enrolled after amendment removing dose escalation option, had their first response evaluation after cycle 3.

All patients who initiated treatment with cabozantinib were evaluable for safety and toxicity from first treatment dose. Adverse event grading was per the Common Terminology Criteria for Adverse Events v 4.0.

Endpoints

Study had coprimary endpoints of investigator-assessed 12-week PFS and response rate (RR) per RECIST v1.1.

Statistical analysis

In initial design, patients were enrolled to an experimental cohort of serous, endometrioid, and mixed histology endometrial cancer, employing a standard Simon two-stage design to evaluate for coprimary endpoints of objective RR and 12-week PFS. Target accrual in stage I was 24 patients, and observation of ≥ 4 PRs or ≥ 8 patients with 12-week PFS, was required to proceed to second stage to accrue a total of 42 patients. The parallel exploratory cohort of uncommon histology cancers would be analyzed independently.

At stage I review, with observed activity across several histologic types and brisk patient accrual, design was modified for stratification

by histologic subtype (serous vs endometrioid) with mixed histology endometrial cancer analyzed in exploratory cohort. In amended trial design, 18 patients each of serous and endometrioid subtype were enrolled in stage I, and observation of ≥3 responses or ≥7 patients with 12-week PFS would be sufficient to proceed to target accrual of a total of 36 patients per cohort. Observation of ≥8 PRs or ≥16 patients with 12-week PFS in a cohort of 36 patients would be considered a signal of clinically relevant activity with each cohort being reviewed independently.

Modified trial design discriminated between coprimary endpoints of objective RR of 30% (vs 10%) and 12-week PFS of 55% (vs 30%). The design had 86% power to detect a true objective RR of at least 30% and at least 90% power to detect a true 12-week PFS rate of at least 55% (or a median PFS of 3.4 months).

Patients with uncommon histology cancers (clear cell, carcinosarcoma, adeno-squamous etc.) were treated in a separate exploratory cohort with planned accrual of 30 patients. Observation of >4 of 10 objective responses in a given subtype was considered activity to warrant further evaluation.

Kaplan–Meier analysis and log-rank test were used to compare PFS across subgroups with different mutation status and Fisher exact test was used to test association between mutation status and response. Because these analyses were exploratory there was no correction for multiple comparisons.

This trial was registered with ClinicalTrials.gov, NCT01935934.

Molecular analyses

All patients consented to molecular profiling of archival tumor tissue. This included somatic and germline variant profiling on formalin-fixed, paraffin-embedded (FFPE) samples using the Next-Generation Sequencing TruSeq Amplicon Cancer Panel on MiSeq platform (one patient had Sequenom MassArray profiling). Gene variants included in these panels are included in Supplementary Table S1 and variant classification was completed as per OncoKB. Profiling was conducted in the Clinical Laboratory Improvement Amendments–certified research laboratory at the Princess Margaret Cancer Centre (Toronto, Ontario, Canada) as described previously (25, 26). FISH for *MET* amplification was performed on FFPE sections using a dual-color DNA FISH probe (Vysis MET Spectrum Red FISH Probe Kit and CEP7 AlphaSatellite DNA Spectrum Green (Abbott Molecular). Fields with at least 50 tumor cells were captured to analyze 100 nonoverlapping tumor cell nuclei to calculate a ratio of *MET* to CEP7 signal; *MET* amplification was defined as MET/CEP7 ratio ≥2. Specimens for FISH were processed at the Princess Margaret Drug Development Program Biomarker Laboratory.

Results

Between May 2013 and November 2016, 103 patients were screened, one patient was deemed ineligible and 102 patients were registered. This included 70 patients in the experimental cohort and 32 in the rare histology, exploratory cohort. Analysis presented is as of April 2019 and all patients are now off trial. Trial profile is outlined in **Fig. 1**.

All patients who initiated treatment were considered evaluable for both treatment response and toxicity. This included four patients with violations of inclusions/exclusion criteria; >2 lines chemotherapy ($n = 2$; both in serous cohort), and uncontrolled hypertension at baseline [$n = 2$; one each in endometrioid and exploratory (carcinosarcoma) cohorts, respectively].

Baseline characteristics of all patients accrued are outlined in **Table 1**. Median age was 64 years (range, 25–84). The majority of women (98%) were good performance status (≤ ECOG 1). Sixty-one percent had prior pelvic radiotherapy and all patients had received prior chemotherapy, (80%: first-line, 20% ≥2 lines).

Experimental cohort outcomes

In endometrioid cohort, we observed five PRs (14%) and 24 patients (67%) achieved 12-week PFS. Median PFS was 4.8 months [95% confidence interval (CI), 4.4–6.4 months] with a 6-month PFS rate of 43% (95% CI, 27%–59%). With the caveat that study did not include a centralized expert pathology review, median PFS in women with grade 1 tumors was 6.4 months (4.7 months–NR), with grade 2 was 5.5 (2.5–10.8) months, and grade 3, 4.3 (1.0–4.8) months. Among the serous histology patients, there were four PRs (12%) and 19 patients (56%) met the 12-week PFS endpoint. Median PFS was 4.0 months (95% CI, 2.8– 4.7 months) with a 6-month PFS of 30% (95% CI, 16%–47%). Of all patients meeting the 12-week PFS, more than half (23/43 patients) remained progression free at their subsequent (20-week) scan.

Median PFS of all patients in experimental cohort (serous and endometrioid histology cancers) was 4.6 months (95% CI, 3.7–4.9 months) with a 6-month PFS rate of 37% (95% CI, 26%–48%). These estimates are based on observation of 67 events from 70 patients in experimental cohort.

Exploratory cohort outcomes

Thirty-two patients were accrued to the rare histology exploratory cohort. This cohort included patients with carcinosarcoma ($n = 19$), clear cell ($n = 5$), mixed ($n = 6$), mucinous ($n = 1$), and adenosquamous ($n = 1$). Across all patients in the exploratory cohort, two patients had PR as their best response (one patient with carcinosarcoma and one with a mixed histology endometrial cancer), and 15 patients achieved a 12-week PFS endpoint, five of whom remained progression free at subsequent (week 20) scan. Within the carcinosarcoma cohort, one patient achieved PR (5%) and eight patients met 12-week PFS (42%). Median PFS for both the whole-exploratory cohort and the carcinosarcoma subgroup was 3.0 months (95% CI, 2.5–4.6 months). The patient with carcinosarcoma who had a PR on treatment had a PFS of 6.7 months.

Figure 2 summarizes antitumor activity of cabozantinib in both experimental and exploratory cohorts. Waterfall plots (**Fig. 2A** and **D**) illustrate tumor response and swimmers' plots (**Fig. 2B** and **D**) time on treatment, color-coded for different histology patients. Median PFS is presented for experimental (Fig. 2C) and exploratory (**Fig. 2F**) cohorts in accompanying graphs.

Safety and adverse events

Cabozantinib-related toxicity was mostly manageable. Adverse events were primarily grade 1–2 in severity, and the most common toxicities of fatigue, hypertension, diarrhea, and hand–foot syndrome responded well to conservative treatment and dose reduction. After experiencing an adverse event, 53 patients (52%) continued on study at daily dose of 40 mg, of these 14 patients required a further dose reduction to 20 mg.

Relevant toxicities experienced by all patients ($n = 102$) who received at least one dose of cabozantinib are outlined in **Table 2**, with a focus on treatment-related toxicities experienced by ≥10% patients. Also included are adverse events of special interest based on the antiangiogenic mechanism of action of cabozantinib including perforation/fistula events, thromboembolism, and bleeding.

Among 102 patients, 21 patients discontinued treatment due to an adverse event. Upon review, one of the 11 was ineligible due

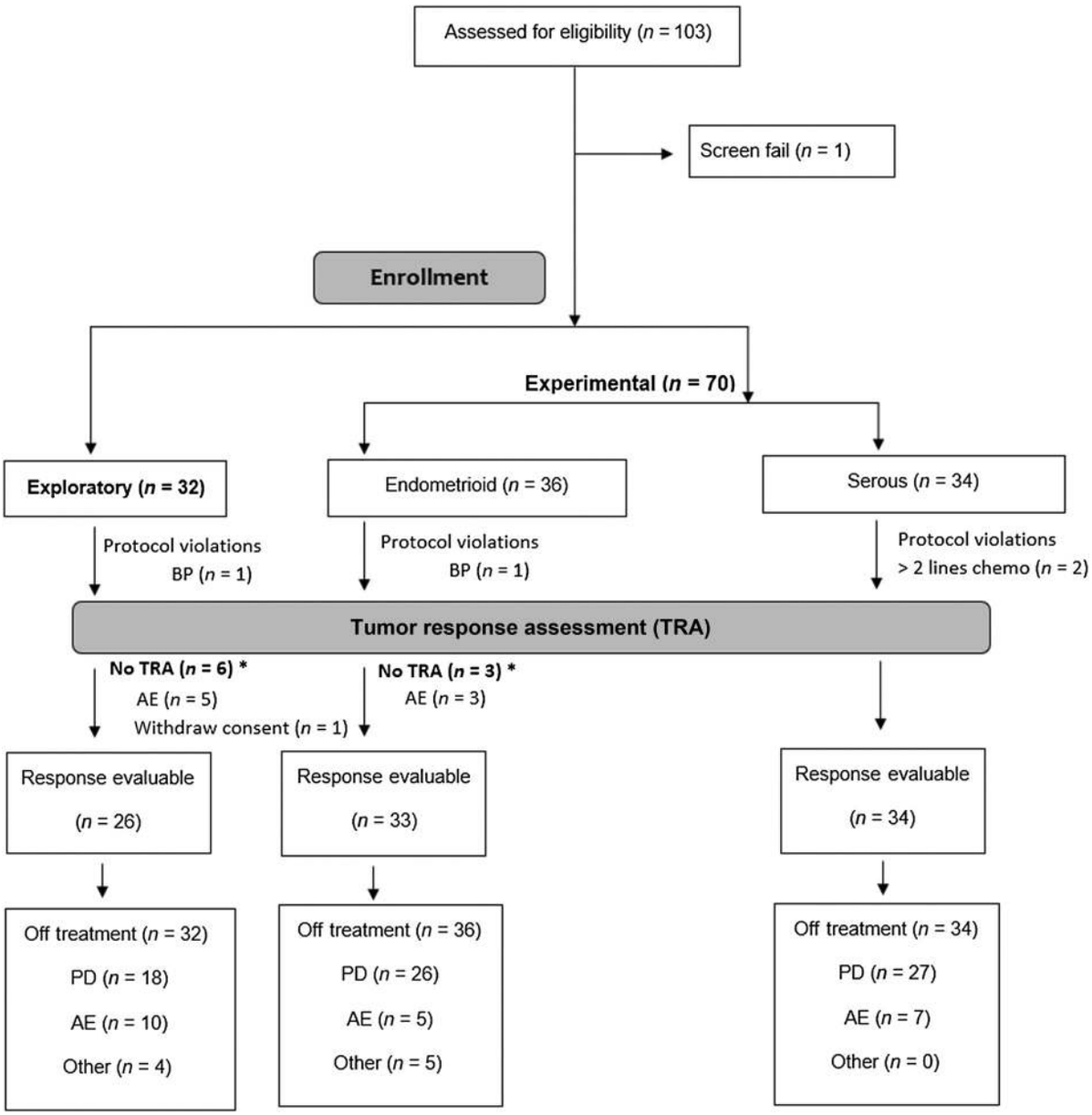

Figure 1.

CONSORT diagram outlining patients enrolled in both experimental and exploratory cohorts. *, identifies patients who discontinued study treatment prior to formal response evaluation (ie, tumor response assessment or TRA): in the exploratory cohort, this included six patients, five who discontinued treatment due to adverse events (AEs) and one who withdrew consent. In the endometrioid cohort, this included three patients with AEs. "Off-treatment" box outlines reasons why patients discontinued the study with "PD": progressive disease; "AE": adverse event; and "other" including withdrawal of consent, physician preference, and intercurrent illness.

to a protocol violation (of inclusion/exclusion criteria) with poorly controlled hypertension at baseline. Another patient was identified as having a clinically occult, but radiographically detected, fistula on baseline imaging. Both were considered to have discontinued treatment due to exacerbation of these baseline conditions in cycle 1. Adverse events experienced by the remaining 19 patients, included colonic fistula/perforation ($n = 8$), thromboembolism ($n = 3$), pain ($n = 2$), hypertension ($n = 1$); sepsis ($n = 1$), malnutrition ($n = 1$), dermatologic toxicity ($n = 1$), weight loss ($n = 1$), and hemothorax ($n = 1$); these adverse events were in the context of disease progression in four patients. One patient died of complications of a colonic fistula. Furthermore, six patients died on study but with evidence of disease progression; these deaths were deemed to be disease related.

Somatic genomic profiling

Archival tumor was available in 91 patients. Genomic analysis failed in seven. Of the remaining, 84, 83 tumors were profiled on the

Table 1. Baseline characteristics of all enrolled patients.

	Total Patients Accrued $n = 102$			
	Experimental $n = 70$		Exploratory $n = 32$	
	Endometrioid $N = 36$	Serous $N = 34$	Carcinoma $N = 19$	Other $N = 13$
Median age (range)	61 (38–84)	68 (39–77)	64 (25–75)	63 (35–74)
ECOG PS				
0	22	16	10	6
1	13	17	9	7
2	1	1		
Chemotherapy				
1 line	33	23	16	10
2 lines	3	9	3	3
>2 lines	0	2	0	0
Pelvic radiotherapy				
Yes	23	19	11	9
No	13	15	8	4
Histologic details				
Grade 1	5	0	0	0
Grade 2	14	0	0	0
Grade 3	14	0	0	0
Unknown	3	34	19	13

NGS TruSeq amplicon panel and 1 on Sequenom (**Fig. 3A**). Among endometrioid cancers ($n = 31$), most commonly observed mutations were *PTEN* ($n = 13$; 42%), *PIK3CA* ($n = 10$; 32%), *CTNNB1* ($n = 9$; 29%), *KRAS* ($n = 8$; 29%), and *TP53* ($n = 6$; 19%). In serous cohort ($n = 30$), most commonly observed mutations were *TP53* ($n = 19$; 58%), *PIK3CA* ($n = 10$; 38%), and *KRAS* ($n = 3$; 12%). Carcinosarcoma tumors ($n = 15$) demonstrated high rates of somatic *TP53* ($n = 7$; 47%), *PIK3CA* ($n = 6$; 40%), and *KRAS* ($n = 3$; 20%) mutation (**Fig. 3B**). No *MET* mutations were documented across all tumors profiled.

There was an interesting trend of high frequency of responses in two patient cohorts with unique molecular contexts. The first group was patients with somatic *CTNNB1* mutation. In this group of 10 patients, we observed a 40% RR ($n = 4$) and 70% 12-week PFS rate ($n = 7$). Two patients were on treatment for over 12 months, and median PFS (of the cohort of 10 patients) was 7.6 months. In the second group of 12 patients with concurrent somatic *KRAS* and *PTEN* or *PIK3CA* mutations, we observed a 25% RR ($n = 3$) and 83% 12-week PFS rate ($n = 10$), median PFS of this cohort of 12 patients was 5.9 months. Disease control in these molecular subgroups in comparison with the remainder of the cohort is illustrated in spider plots in **Fig. 4**. In spite of these intriguing trends, these higher RRs were not statistically significant in comparison with responses observed in the full patient cohort.

In addition to profiling genomic variants, the first 29 patient tumors (which included 12 endometrioid, 12 serous, four carcinosarcoma, and one mixed-histology tumor) were evaluated for *MET* amplification by FISH. In this subset, there was no evidence of *MET* amplification; although two patient tumors did have small clones of amplification, with cMET/CEP7 ratio of 1.55, this was not significant.

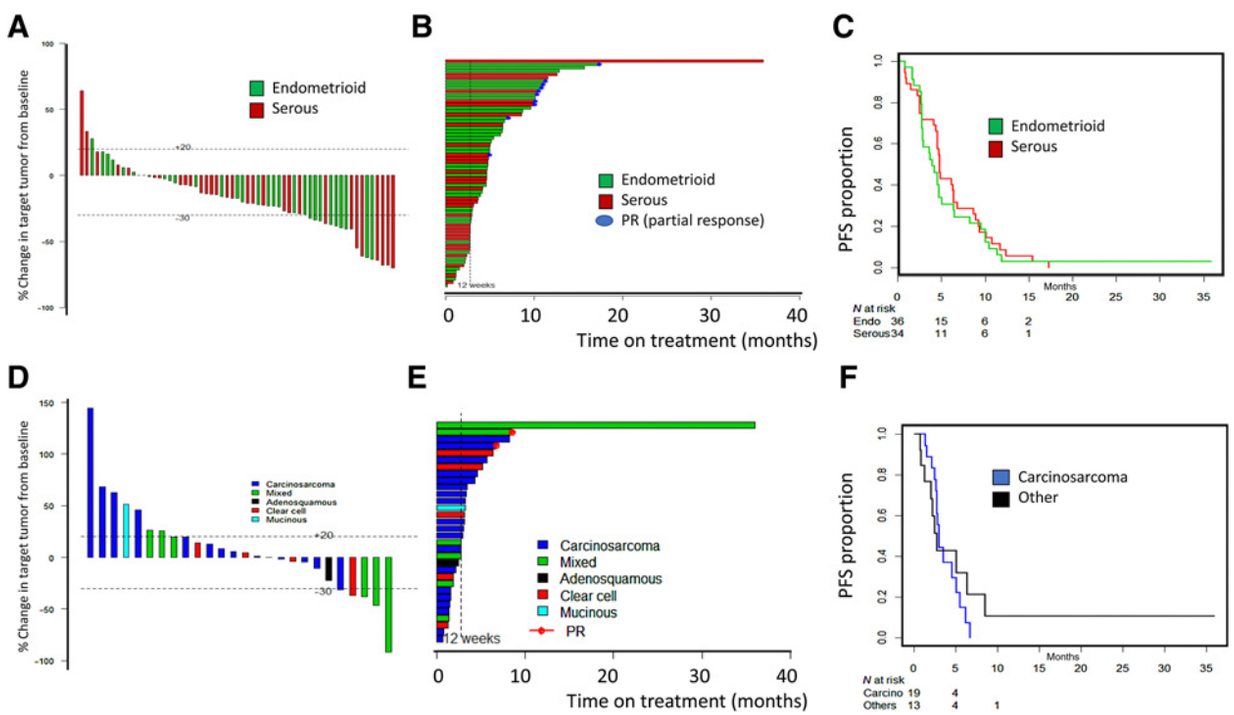

Figure 2.

Summary of activity of cabozantinib. Summary of activity of cabozantinib in both experimental (**A–C**) and exploratory (**D–F**) patient cohorts. **A** and **D,** Objective tumor responses with dotted lines indicating boundaries for stable disease. **B** and **E,** Time on treatment, with dotted line highlighting 12-week timepoint. Patients who also achieved a PR on study are indicated in blue (**B**) or red (**E**), respectively. **C** and **F,** PFS in experimental and exploratory cohorts color-coded for tumor subgroups.

Table 2. Treatment-related adverse effects.

	No. of patients affected ($n = 102$)				
Adverse event	**< Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Constitutional					
Fatigue	62	3	0	0	65
Anorexia	47	2	0	0	49
Weight loss	27	4	0	0	31
Vascular					
Hypertension	26	25	1	0	52
Gastrointestinal					
Diarrhea	52	8	0	0	60
Nausea	44	2	0	0	46
Dysgeusia	42	0	0	0	42
Mucositis	38	0	0	0	38
Vomiting	19	0	0	0	19
Gastroesophageal reflux	17	0	0	0	17
Dyspepsia	13	0	0	0	13
Dry mouth	15	0	0	0	15
Abdominal pain	16	3	0	0	19
Dermatologic					
PPED	40	0	0	0	40
Dry skin	11	0	0	0	11
Pruritus	10	0	0	0	10
Alopecia	12	0	0	0	12
Hematologic					
Anemia	22	5	0	0	27
Leukopenia	33	0	0	0	33
Lymphopenia	23	7	1	0	31
Neutropenia	22	1	0	0	23
Thrombocytopenia	18	1	1	0	20
Biochemical					
AST increased	61	4	1	0	66
ALT increased	55	8	1	0	64
Hypomagnesemia	45	3	0	0	48
Hypophosphatemia	25	5	0	0	30
ALP increased	22	1	1	0	24
Hypoalbuminemia	28	1	0	0	29
GGT	13	4	0	0	17
Hyponatremia	18	1	2	0	21
Hypokalemia	15	5	0	0	20
Hypocalcemia	19	0	0	0	19
Hyperbilirubinemia	11	0	1	0	12
Increased lipase	9	3	0	0	12
Proteinuria	12	0	0	0	12
Other					
Hypo/hyperthyroidism	12	0	0	0	12
Hoarseness	15	0	0	0	15
Extremity pain	11	0	0	0	11
Headache	11	0	0	0	11
Special interest AEs					
Bleeding: other	11	1	0	0	12
GI bleed	2	1	0	0	3
Thromboembolism (venous)	5	5	1	0	11
Thromboembolism (arterial)	1	0	0	0	1
GIPF	2	3	3	0	8

Note: Treatment-related adverse events experienced by >10% all patients treated ($n = 102$), including serious adverse events of interest.
Abbreviation: AE, adverse event; GIPF, GI perforation/fistula; PPED, palmar-plantar erythrodysesthesia.

Discussion

In this large, single-arm study, we observed activity of cabozantinib in both patients with serous and patients with endometrioid endometrial cancer who have experienced disease progression after platinum-based chemotherapy. In addition to the coprimary endpoints of response rate and 12-week PFS, we also evaluated the 6-month PFS rates, as per recent consensus guidelines (27). In our cohort of serous/endometrioid endometrial cancer, disease control reflected by 12-week PFS rates of 59%–66%, and 6-month PFS rates of 29%–40%, is encouraging compared against a historical 6-month PFS of less than 20% and aligns favorably against that of agents evaluated previously (28, 29). Furthermore, treatment-related toxicities were primarily ≤ grade 2 with few ≥ grade 3 events, most of which were manageable with conservative measures and dose reductions. The percentage of patients who required dose reduction aligns with reports of similar strategies in this disease (30). The majority of patients discontinued therapy for disease progression. Of 102 patients treated, 22 discontinued treatment for adverse events, five of whom also had disease progression. There were, therefore, 17 patients (17%) who discontinued for treatment-related toxicity. That six patients continued on cabozantinib for longer than 12 months also speaks further to the tolerability of this regimen.

Women with nonserous/nonendometrioid endometrial cancer are often excluded from clinical trials. Through our exploratory cohort, we were able to characterize the molecular features of these rare histology endometrial cancers. We observed similar somatic genomic aberrations in uterine carcinosarcomas as in serous and endometrioid endometrial cancer, aligning with recent reports (31). These observations provide further justification to evaluate targeted agents like cabozantinib across the histologic and molecular spectrum of endometrial cancer. Not surprisingly, patients with carcinosarcoma in our exploratory cohort had an especially poor prognosis. We observed a PR rate of 7%, 12-week PFS of 42%, and 3-month median PFS, somewhat encouraging in comparison with results of pazopanib in carcinosarcoma endometrial cancer, where no PRs were observed and median PFS was 2 months (32). We remain cognizant, however, that these outcomes remain dismal and that these patients experienced a high frequency of GI perforation/fistula (GIPF) events, which may be reflective of disease burden. Still, we feel that there are some preliminary signals of activity that warrant further evaluation, potentially in earlier stages of disease for this patient cohort with aggressive tumor behavior and few available options.

One serious adverse event of significance is that of GIPF, which affected 6% serous/endometrioid patients and 16% patients in exploratory cohort. These hazards are reminiscent of the early evaluation of bevacizumab in ovarian cancer (33) and more recent studies in endometrial cancer (18). Although smaller trials of other antiangiogenics have noted lower frequency of these events, the lower number of patients treated must be considered in these observed risks (12, 30). The four-patient group in experimental cohort, who developed GIPF, includes one patient with unrecognized fistula on baseline imaging, highlighting the importance of careful radiologic review of patients with bowel involvement from recurrent endometrial cancer. Two had received prior (external beam pelvic) radiotherapy and there was no observed correlation between prior radiation and fistula development. None of the five patients in the exploratory cohort who developed GIPF had received prior radiotherapy. Half of GIPF events were in the context of confirmed or suspected progression. A randomized evaluation in a larger cohort would better delineate cabozantinib-related toxicity from disease-related events and we feel is justified on the basis

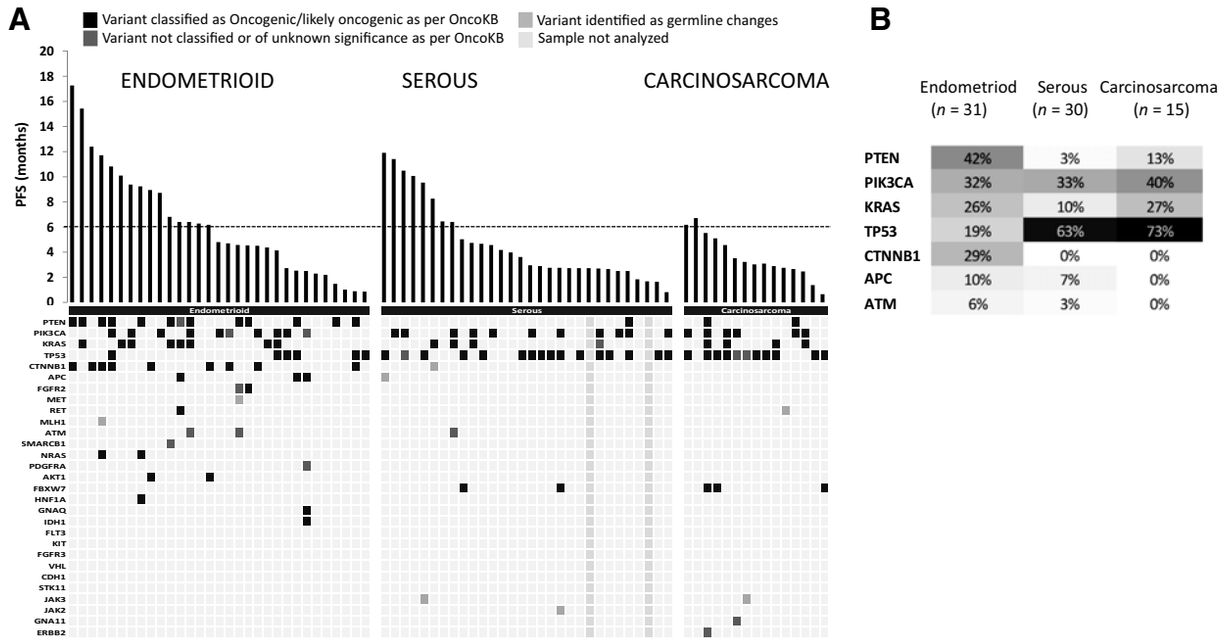

Figure 3.
Summary of somatic profiling of endometroid, serous, and carcinosarcoma histology endometrial cancer patient treated with cabozantinib. **A,** profiling data is aligned with patient progression-free-survival (months) with variants as indicated (oncogenic/likely oncogenic variants in black, variant of unknown significance in dark grey, and germline changes in light grey). **B,** heatmap summarizing frequencies of common mutations in this patient cohort.

of the preliminary signals of activity observed here. Furthermore, incorporating formal patient-reported outcome measures in a randomized evaluation would provide important insights into the potential impact of this treatment on patient quality of life.

Although cabozantinib has demonstrated efficacy across different tumor types, molecular markers predictive of response have been elusive; several studies have been unable to establish a robust relationship between *MET* expression status and tumor response (34, 35). We initially explored a potential relationship between *MET* amplification and response. In a preliminary assessment of a subset of 29 tumors across different histologies, we identified no tumors with *MET* amplification, aligning with data in publicly available databases where frequency of *MET* amplification was <1% (36, 37). Recognizing that MET was likely a poor candidate biomarker of response in this setting

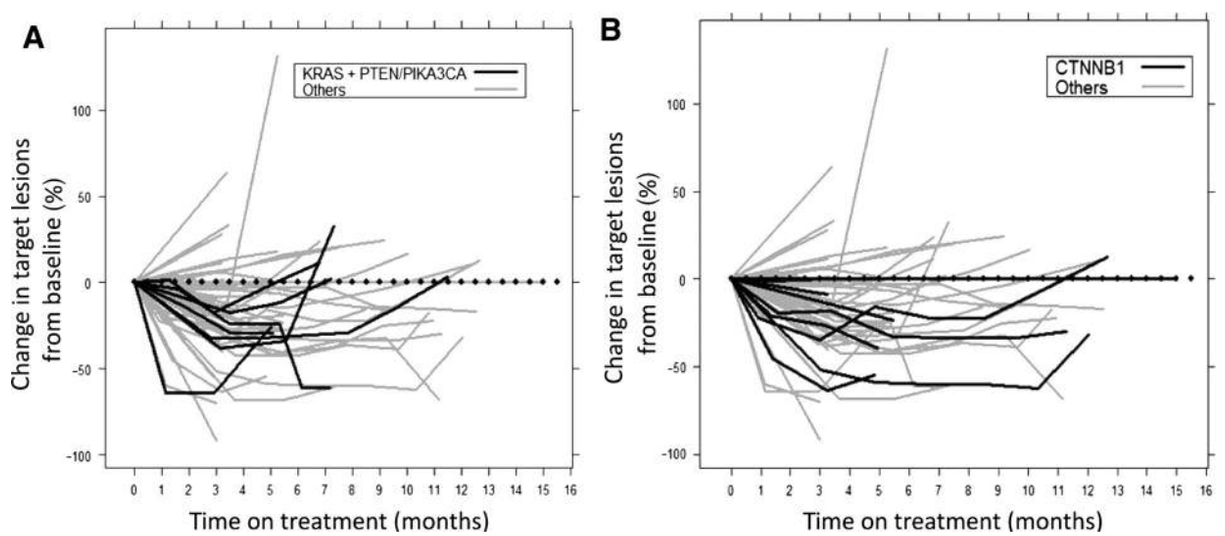

Figure 4.
Spider plots illustrating activity of cabozantinib in (**A**) patients with KRAS + PTEN/PIK3CA-mutated tumors (black) versus all others (grey); and (**B**) patients with CTNNB1-mutated tumors (black) versus others (grey).

we discontinued this line of investigation to prioritize scarce tumor tissue for other correlative molecular studies.

We completed profiling of archival tumor samples using a 48-gene panel encompassing genes relevant to endometrial cancer pathogenesis and *MET* signaling (see Supplementary Table S1 for details). No *MET* mutations were documented, aligning with previous reports (38). Together with the lack of MET amplification observed, it would seem that aberrant *MET* function is not a major determinant in predicting cabozantinib sensitivity in endometrial cancer, unless driven through other pathways.

We did observe a trend of increased clinical benefit in two discrete molecular cohorts of patients. The first group included patients with somatic *CTNNB1* mutation. *CTNNB1* mutations have long been implicated as an early event in endometrial carcinogenesis, appearing limited to endometrioid histology cancers (39). An interesting analysis integrating genomic and proteomic profiling identified *CTNNB1* mutations in young women with obesity who, despite an initial presentation with early-stage disease, had inferior overall survival in comparison with women diagnosed with similar stage/grade of disease but lacking *CTNNB1* mutation (40). Furthermore, *in vitro* and *in silico* analyses have linked *CTNNB1* mutation with increased angiogenesis (41), providing mechanistic rationale for observations from GOG-86P, where *CTNNB1* mutation identified a subgroup of patients who benefited from the addition of the antiangiogenic bevacizumab to carboplatin/paclitaxel (42). Given the recognized poor prognosis of patients harboring somatic *CTNNB1* mutation, our exploratory observations of a PR rate of 40% and median PFS of 7.6 months in this small cohort of 10 patients is encouraging and warrants further evaluation, ideally in a randomized trial setting.

The second cohort of interest included patients with tumors harboring concurrent *KRAS* and *PTEN* or *PIK3CA* mutations. This finding aligns somewhat with one made in medullary thyroid cancer, where patients with tumors with *RET* or *RAS* mutation had a survival benefit with cabozantinib (43). This is particularly interesting in endometrial cancer given the prominence of RAS/MAPK pathway activation in this disease. Furthermore, although RET mutation is a rare occurrence (ref. 44; we detected *RET* mutation in one patient tumor), other mechanisms of RET pathway dysregulation, occult to traditional panel profiling, have been characterized in endometrial cancer and may be relevant in the context of dependence on proangiogenic signaling (45). Again, we highlight the fact that these analyses were not prespecified and are best exploratory and hypothesis generating; still, given the biological plausibility and intriguing trends, we believe these potential relationships warrant further evaluation in a larger randomized trial.

There remain a few limitations of this work. A centralized review by an expert gynecologic oncology pathologist was not included and may have identified discrepancies in histotype and grading of some patient tumors. Furthermore, contemporary strategies of somatic profiling based on exome or whole-genome sequencing, are more comprehensive than the targeted hot spot panels that were in common use at the time this study was conducted. We recently described discrepancies in identification of TP53 mutation in high-grade serous ovarian cancer using targeted sequencing versus standard IHC (46). It is likely that both histologic misclassification and the use of less sensitive sequencing approaches both contributed to the lower than anticipated rate of TP53 mutation (63%) in our serous histology cohort. Finally, correlative molecular studies were completed in archival tumor samples, which may not accurately reflect the mutational status of tumors at time of recurrence and after treatment with chemotherapy or radiation (47). We feel that the correlative work completed in this study however, provides some interesting avenues for further consideration, and suggest that future studies in this area employ more in-depth tumor characterization, including status of mismatch repair genes, fusion genes, and quality of immune infiltrate, in baseline tumor biopsies for a higher yield with respect to identifying candidate biomarkers.

In conclusion, cabozantinib has single-agent activity with acceptable toxicity across the molecular spectrum of endometrial cancer. Although a clear predictive biomarker of response remains to be determined, the data suggests that patients whose tumors harbor aberration in either *CTNNB1* or both MEK and PIK3CA/AKT pathways might be more sensitive to this treatment approach. Our study adds to the body of literature to support a benefit to targeting angiogenesis in endometrial cancer (30).

Disclosure of Potential Conflicts of Interest

H.W. Hirte reports receiving speakers bureau honoraria from AstraZeneca and Merck, and reports receiving other remuneration from Merck for expert testimony. M.O. Butler is an employee/paid consultant for Merck, Bristol-Myers Squibb, Novartis, Immunocore, and GlaxoSmithKline, and reports receiving commercial research grants from Takara. G.F. Fleming reports receiving commercial research grants from Merck, Genentech, Tesaro, Corcept, Eisai, Abbvie, Hoffman La Roche, Compugen, Incyte, 47 Inc., Syndax, Iovance, Syros, Astex, Sanofi, and Sermonix, reports receiving other commercial research support from Corcept, reports receiving speakers bureau honoraria from Curio Science/Vaniam, and is an advisory board member/unpaid consultant for Abbvie and TTC Oncology. J. Hurteau is an employee/paid consultant for GlaxoSmithKline. K. Matsuo reports receiving speakers bureau honoraria from Chugai, and reports receiving other remuneration from Springer and VBL Therapeutics. D. Matei is an employee/paid consultant for Radius Inc., Roche, AstraZeneca, and Tesaro. M. Cristea is an employee/paid consultant for Abbvie and AstraZeneca, and reports receiving speakers bureau honoraria from AstraZeneca. S. Lheureux is an employee/paid consultant for AstraZeneca, and reports receiving speakers bureau honoraria from AstraZeneca, GlaxoSmithKline, Roche, and Merck. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

This study was supported by funding through N01 Phase II consortium contract (HHS N261201100032C). Correlative studies were funded through an Ontario Institute of Cancer Research Translational Research Team grant. The authors would also like to gratefully acknowledge the contributions of Dr. Swati Garg, Princess Margaret Cancer Centre, toward genomic analyses.

The study was funded through the N01 phase II consortium contract (HHS N261201100032C). Molecular analyses were funded independently through grant

funding from Ontario Institute of Cancer Research and Princess Margaret Cancer Centre Foundation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 11, 2019; revised December 10, 2019; accepted January 24, 2020; published first January 28, 2020.

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