Published in final edited form as:

Gynecol Oncol. 2015 September ; 138(3): 513–518. doi:10.1016/j.ygyno.2015.07.006.

A Phase II Trial of Trebananib (AMG 386; IND#111071), a Selective Angiopoietin 1/2 Neutralizing Peptibody, in Patients with Persistent/Recurrent Carcinoma of the Endometrium: An NRG/Gynecologic Oncology Group Trial

Kathleen N. Moore, MD¹, Michael W. Sill, PhD², Meaghan E. Tenney, MD³, Christopher J. Darus, MD⁴, David Griffin, MD⁵, Theresa L. Werner, MD⁶, Peter G. Rose, MD⁷, and Robert Behrens, MD⁸

¹ Stephenson Oklahoma Cancer Center, 800 NE 10th Street, OKC, OK 73104

² NRG Oncology Statistics & Data Management Center; Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 msill@gogstats.org

³ University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637 mtenney@babies.bsd.uchicago.edu

⁴ Maine Medical Center, 102 Campus Drive Unit 116, Scarborough, ME 04074 darusc@mmc.org

⁵ Upstate Carolina CCOP Oncology Research, 101 East Wood Street, Spartanburg, SC 29303 david_griffin@bshsi.org

⁶ Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Salt Lake City, UT 84112 theresa.werner@hci.utah.edu

⁷ Cleveland Clinic Foundation, 9500 Euclid Avenue; A81; Cleveland, OH 44106 rosep@ccf.org

⁸ Cancer Center of Iowa, Iowa Wide Oncology Research Coalition, 1221 Pleasant Street, suite 450; Des Moines IA 50309 rbehrens@cancercenterofiowa.com

Abstract

Objectives—Ang1&2 (angiopoietin-1; -2) interact with Tie2 receptors on endothelial cells to mediate vascular remodeling in an angiogenesis signaling pathway distinct from the VEGF axis. Trebaninib is a peptide Fc fusion protein that binds Ang1 and 2 and prevents interaction with Tie2. The efficacy of trebananib in recurrent/persistent endometrial cancer (EC) was studied.

Corresponding Author: Kathleen N. Moore, MD, Stephenson Oklahoma Cancer Center, 800 NE 10th Street, Oklahoma City, OK 73104, Phone 405-271-8707, Fax 405-271-2976, Kathleen-Moore@ouhsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICTS OF INTEREST

Dr. Kathleen Moore is on the advisory board for Astra Zeneca, Genentech/Roche, Immunogen, Advaxis, and Amgen. Dr. Theresa Werner reports research support to the institution for clinical trials from AbbVie, Bayer, Novartis, and Roche-Genentech. All other co-authors have no conflicts to declare.

Methods—The primary objective was to determine the frequency of patients with objective tumor responses (ORR) and event-free survival for 6 months (6-month EFS) and determine toxicity of trebananib at a dose and schedule of 15mg/kg, IV QW. Recurrent/persistent EC, measurable disease, and 2 prior chemotherapy lines were required.

Results—Thirty-two patients were eligible and treated. The most common histologies were G1/2 endometrioid (31%), G3 endometrioid (28%) and serous (31.3%). 78% of patients had 1 prior regimen. Patients received 1-9+ cycles of trebananib; 24 patients (75%) received 2 cycles. One patient had a partial response (3.1%); 8 patients had stable disease (25%) and 5 patients (15.6%) had 6 month EFS. Median progression-free survival and overall-survival were 1.97 months (90% CI 1.77-2.1) and 6.6 months (90% CI 4.01-14.75), respectively. Most common adverse events (AE) were fatigue, anemia, and GI issues. Grade 3 and 4 AEs were: GI 31 and 0%; Vascular 22 and 0%; Metabolism/nutrition 19 and 3%; General (including edema) 16 and 0%.

Conclusions—Trebananib has insufficient single agent activity in recurrent EC to warrant further investigation at this dose/schedule.

Keywords

endometrial cancer; angiogenesis; trebananib

INTRODUCTION

Endometrial cancer will affect 54,870 women in the United States in 2015 and will result in 10,170 deaths [1]. For women who present with advanced stage or recurrent disease, not amenable to localized therapies, outcomes are poor. There have been several randomized studies performed by the Gynecologic Oncology Group (GOG) addressing the issue of optimal therapy for this group of patients. These studies have focused on three active agents; doxorubicin, paclitaxel and a platinum given in doublet and triplet combinations. GOG-0209 established paclitaxel and carboplatin as the standard of care in a non-inferiority trial. [2-4] It is striking that among these phase III trials, for those patients who enter with measurable disease, the complete clinical response rate ranges from . 10.8 (GOG 209) to 22% (GOG 177) indicating that the vast majority of these patients will progress while on therapy.

There are no standard options available at the time of subsequent recurrence or progression. Hormonal therapies, when given to chemotherapy naïve patients can result in response rates of up to 33%, but responses are of short duration (median PFS of approximately 3 months) and of smaller effect size when given to previously treated patients[5-9].

Efforts to identify additional active agents to use for patients when they progress/recur following combination cytotoxic therapy have been largely disappointing. The GOG-129 series evaluates cytotoxic agents in patients with one prior cytotoxic regimen and has tested and published on 13 different agents with only one meeting the 15% response rate bar for further accrual. This study, 129C evaluated paclitaxel and reported a response rate of 25% but this was in a treatment era before paclitaxel was used as upfront therapy and so expectations of this response being seen with current use of paclitaxel as primary therapy are low [10-22].

Thus far, published/presented outcomes for 11 phase II trials exploring targeted agents in the setting of recurrent disease following primary chemotherapy are available. These trials evaluated agents targeting the epidermal growth factor receptor pathway (GOG 229D and 229C) [23,24], MEK1/2 (GOG 229H) [25], but predominantly this series of trials has focused on anti-angiogenesis agents with varying success [26-33].

The earliest exploration of anti-angiogenesis agents in endometrial cancer was a phase II GOG study of thalidomide in refractory endometrial cancer which demonstrated an association between elevated plasma vascular endothelial growth factor (VEGF) levels and poor prognosis [26]. Other studies reported VEGF receptor (VEGFR) was found to be present in up to 2/3 of endometrial adenocarcinoma specimens, and VEGF expression was higher in endometrial adenocarcinoma than in normally cycling endometrium [34,35]. Single agent bevacizumab, a monoclonal antibody directed against VEGF-1 has been studied by the GOG in study 229E with an RR of 13.5% and 40% were progression-free at 6 months [27]. Also targeting the VEGF pathway but via tyrosine kinase inhibition were phase II studies of brivanib (GOG 229I) and cedirinib (GOG 229J) which demonstrated an overall RR of 19% and 12.5% respectively and 30% and 33.3% respectively remained progression-free at 6 months [30].

While much of the interest in targeting angiogenesis has focused on the VEGF pathway, the Angiopoietin (Ang) Tie (Ang-Tie2) pathway is also an important potential target. Ang2 is up-regulated at sites of angiogenesis [36]. Ang1 is thought to promote recruitment of pericytes to vascular tubes, thereby helping to establish and maintain the interaction between endothelial cells and perivascular support cells. Ang2 was initially identified as a naturally occurring antagonist for Ang1 and Tie2 and appears to compete with Ang1 and Tie2 binding and reduces vascular integrity perhaps making the endothelial cells more responsive to the proliferative signals of VEGF [37,38].

Ang1 and Ang2 binding to Tie2 mediate vascular remodeling and trebananib (formerly AMG 386) is an Fc fusion peptibody that prevents Tie2 receptor activation through binding of both Ang1 and Ang2 [39]. Trebananib has shown anti-angiogenesis activity in pre-clinical models of endometrial cancer [40] and has single agent activity in a phase I trial up to doses of 30mg/kg including an ovarian cancer patient with a durable partial response at this highest dose. [41] Recently, a randomized phase 3 trial comparing weekly paclitaxel (80mg/m²) and placebo to weekly paclitaxel and trebananib (15mg/kg) in women with platinum resistant ovarian cancer (TRINOVA-1) was published reporting a statistically significant prolongation in PFS for the trebananib group (7.2 months (5.8-7.4) vs. 5.4 months (4.3-5.5) respectively, hazard ratio 0.66, 95% CI 0.57-0.77, p<0.0001) [42]. It is important to note that addition of trebananib, in addition to improving PFS, did so with a different toxicity profile than VEGF directed therapies. This may provide an alternative anti-angiogenic strategy for those patients who cannot tolerate VEGF targeted side effects but may gain benefit in terms of tumor control and warrants investigation.

Methods

Patient selection

Eligibility criteria for enrollment on this study (NCT01210222) can be found online at www.clinicaltrials.gov. All patients had a diagnosis of recurrent or persistent endometrial carcinoma refractory to curative or known effective therapy. All patients were required to sign an institutional review board approved informed consent form prior to any study procedures being performed. All patients had histologic confirmation of the original epithelial primary tumor by the GOG Pathology Committee. All patients were required to have measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [43]; and GOG Performance Status of 0 to 2. Patients may have had up to two prior chemotherapeutic regimens for treatment of endometrial cancer but prior use of biologic or targeted therapies were excluded. All institutions required approval by their local Institutional Review Board before trial initiation.

Treatment

Patients received trebananib 15mg/kg IV every week. A cycle was defined as 28 days (4 weeks). The initial administration was given over 60 minutes and, if well tolerated, subsequent administrations were given over 30 minutes.

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

There were no dose modifications for trebananib during this study. Trebananib administration could be held for up to 14 days for treatment related toxicity after which therapy was discontinued if the toxicity had not resolved. Trebananib administration was discontinued for any grade of CNS hemorrhage or for grade 3 hemorrhage in any other organ. Trebananib administration was also discontinued for symptomatic grade 3 or grade 4 thromboembolic events. Resumption of trebananib following a hold was allowed for asymptomatic grade 3 thromboembolic events, provided that the patient was established on an appropriate anti-coagulation regimen and had no conditions that placed them at high risk of hemorrhage. Trebananib administration was held in the setting of symptomatic grade 2 hypertension or grade 3 hypertension, and could be held for up to 2 weeks while attempting to normalize blood pressure. Trebananib was permanently discontinued with the occurrence of grade 4 hypertension.

Lymphedema was also a toxicity of interest. Trebananib was held with the development of grade 3 lymphedema and could not be restarted until the lymphedema had resolved or returned to patient's baseline.

In addition to specific hold and discontinuation parameters for hemorrhage, thromboembolic events, hypertension and edema, continued dosing was held in the setting of neutropenia (ANC <1500 cells/mcl) or thrombocytopenia (<100,000/ μ l) for a maximum of 2 weeks. In addition, treatment was held for any of the following:

Neuropathy grade 2, renal toxicity grade 2, nausea grade 3 despite maximal supportive care, vomiting grade 3 despite maximal supportive care, diarrhea grade 3, hepatic function abnormalities (AST, ALT and/or bilirubin grade 3 in or other non-hematologic toxicity of CTCAE grade 2 considered at least possibly drug related.

Evaluation Criteria

Response and progression were evaluated via the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [43]. 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 3 months thereafter until disease progression was confirmed. Responses required confirmation at least 4 or more weeks from the initial documentation.

Statistics

The primary objective of the study was to evaluate the efficacy of trebananib through the frequency of patients with objective tumor responses and the frequency who survived event-free for at least 6 months (6-month EFS). The endpoints for EFS were progression, death, or beginning a subsequent therapy. Activity on either scale is worthy of further investigation for phase II studies since they are expected to be useful surrogates for OS.

The null hypothesis (H_0) 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. H_0 jointly specified the probability of a patient experiencing a tumor response to less than or equal to 10% and the probability of a patient EFS for at least 6 months to less than or equal 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 6 months or a 15% increase in the probability of response.

H_0 was evaluated with a flexible method provided by Sill et al.,[44] which is a 2-stage design used to limit patient exposure to inactive regimens.

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 4 and the critical value for the number of patients who were 6-month EFS was 7. 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 be 8 and the critical value for the number of patients with EFS at 6 months would be 12 [44].

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 to 35 (stage 1) and 48 to 55

(cumulatively after stage 2). The expected probability of early termination when the agent is uninteresting was likely between 55% and 62%, depending on the level of association between the two variables. The study had about 90-92% power of detecting a clinically significant effect, depending on the level of association between the primary endpoints [44].

RESULTS

Patient Characteristics

Between June 2011 and August 2012, 35 patients were enrolled onto this phase 2 study. Two of these patients were ineligible and 1 patient never received study treatment, leaving 32 assessable for toxicity and response. Patient characteristics are listed in table 1. The vast majority of patients were 60 years of age (78%) and actually 44% of the cohort were age 70. This study cohort was overwhelmingly Caucasian (91%) and of performance status 0 (56%). Cancer histology included serous (31%), endometrioid grade 3 (28%) and endometrioid grade 1 or 2 in the remaining 31%. The majority of patients had received only 1 prior line of cytotoxic chemotherapy (78%), 43% had received prior radiation and 100% had undergone prior surgery.

Adverse Events

The safety profile of trebananib in recurrent endometrial cancer patients is summarized in Table 2. There were no grade 5 treatment related deaths on this study.

The most common toxicities of any grade reported were fatigue (69%), anemia (53%), constipation (50%), hypertension, nausea and abdominal pain (38%) and limb edema (34%).

Grade 3 toxicities included abdominal pain (8 events), hypertension and nausea (4 events each), ascites (3 events each), vomiting, limb edema, lymphedema, thromboembolic event, fatigue, pain, increased INR, dehydration, hypoalbuminemia, hyponatremia, dyspnea (2 events each), colonic obstruction, rectal pain, ileus, small intestine obstruction, kidney infection, urinary tract infection, prolonged prothrombin time, increased alkaline phosphatase, increased creatinine, decreased lymphocytes, anorexia, hypokalemia and hyperkalemia, hypernatremia, back pain, generalized muscle weakness, urinary tract obstruction, pleural effusion, (1 event each).

There was 1 reported grade 4 hyponatremia.

Efficacy

The efficacy of trebananib in recurrent endometrial cancer is summarized in Table 3. Only 1 patient (3.1%) had a confirmed partial response and 8 patients (25%) had stable disease. The majority of patients (75%) received 2 or fewer cycles of therapy prior to discontinuing. Five patients (15.6%) did receive 9 or more cycles.

The median PFS was 1.97 months and the median OS was 6.6 months. (Figure 1) The probability of PFS at 6 months was 18.8% and the EFS > 6 months was 15.5%. Trebananib did not meet the pre-set statistical thresholds to open to a second stage of accrual and so was closed following first stage accrual.

DISCUSSION

Development of effective therapies for recurrent endometrial cancer has been an elusive target despite efforts across numerous cytotoxic and biologic agents. The response rate for cytotoxic agents ranges from 0-25% with the 25% value corresponding to use of paclitaxel in paclitaxel naïve patients [11]. With this study excluded, response rates range from 0-25% and the probability of PFS at 6 months ranges from 0- 46.9%.

Exploration of biologic efforts has been equally as frustrating with the exception of anti-angiogenesis agents. Thus far, the GOG has published/presented 12 phase II trials evaluating biologic agents in recurrent endometrial cancer. Nine of these 11 trials involve anti-angiogenic agents (table 4) including thalidomide, bevacizumab, aflibercept, combination bevacizumab and temsirolimus, brivanib, nintedanib, dalantercept, cedirinib and now trebananib [26-33]. Among these agents, several appear promising based on response rates and/or proportion of patients remaining PFS at 6 months. Bevacizumab (13.5%), bevacizumab + temsirolimus (24.5%) and brivanib (18.6%) all had response rates that indicated activity in this disease [27,29,30]. More impressively, single agent bevacizumab (40%), aflibercept (41%), combination bevacizumab + temsirolimus (47%), cedirinib (33.3%) and brivanib (30%), had clinically relevant disease control signals by virtue of the proportion remaining disease free at 6 months [27-33]. Enthusiasm for aflibercept is limited by its toxicity profile including 2 deaths possibly related to treatment [28].

Sunitinib, a tyrosine kinase receptor targeting platelet derived growth factor α and β , VEGFR 1, 2 and 3, C-Kit, RET and Flt 3 has been evaluated in a phase II trial enrolling metastatic or recurrent endometrial cancer patients with response rates of 15-18.1% [45]. Sorafenib, a tyrosine kinase inhibitor targeting RAF kinase, VEGFR 2 and 3, platelet derived growth factor β Flt 3, C-kit and RET has been tested in a similar phase II trial with a response rate of only 5% [46].

Unfortunately, trebananib, given as a single agent for advanced/recurrent endometrial cancer did not meet the pre-set statistical bar either by response rate, EFS or percentage PFS at 6 month to indicate activity enough for further study at this time.

It is clear that some anti-angiogenesis agents do have activity in recurrent endometrial cancer. The activity of bevacizumab led to its inclusion in primary therapy concurrent with chemotherapy and as maintenance in patients with chemotherapy naïve advanced/recurrent endometrial cancer (GOG- 86P), the results of which are still pending but if positive, would increase enthusiasm for further exploration of anti-angiogenesis agents in this disease. Importantly, this study included integrated genomic and proteomic characterization of the included patients, 2/3 of whom received an anti-angiogenesis agent and 1/3 of who were exposed to temsirolimus. This will provide the capability to perform correlative studies between the molecular profile of the tumor and outcome among patients who did or did not receive bevacizumab and perhaps identify molecular subtypes best treated with anti-angiogenic strategies.

Future studies of agents such as trebananib in this population would benefit from integral biomarker exploration giving us a better opportunity to identify active drugs. In

TRINOVA-1, preliminary analysis of baseline levels of Ang1, Ang2 and the soluble form of the Tie-2 receptor did not correlate with PFS.[42] Unfortunately, in this study with only 2 responses, no correlative analyses would be possible. A second strategy may be to explore combination therapies. The value in combining trebananib with weekly paclitaxel in TRINOVA 1 may be due to the additive combination of two active agents and/or due to synergistic effects of targeting the angiopoietin Tie interaction in addition to the known anti-angiogenic effects of weekly paclitaxel. The data for weekly paclitaxel in recurrent endometrial cancer is limited, however phase II studies report a response rate of 26.7% (among patients who had received paclitaxel as front line therapy (73%)).[47] Rational combination studies may help us identify superior treatment strategies. With current strategies of enrolling unselected patients to single agent biologics, we may continue to struggle to identify agents with possible benefit.

Acknowledgments

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical Office (CA 37517) and NRG Oncology (1 U10 CA180822). The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: Abington Memorial Hospital, University of Utah Hospital and Clinics, University of Iowa Hospitals and Clinics, Indiana University Hospital, Rush University Medical Center, Case Western Reserve University, Women and Infants Hospital, Carolinas Medical Center/Levine Cancer Institute and Community Clinical Oncology Program.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2015. American Cancer Society; Atlanta: 2015.
2. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2004; 22:3902–3908. [PubMed: 15459211]
3. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2004; 22:2159–2166. [PubMed: 15169803]
4. Miller D, Filiaci V, Fleming G, Mannel R, Cohn D, Matsumoto T, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol.* 2012; 125:771–773. Abstract.
5. Fiorica M, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W, et al. Phase II trial of alternating course of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004; 91:10–14. [PubMed: 14751131]
6. 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; 91:4–9. [PubMed: 14751130]
7. Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 1996; 14:357–361. [PubMed: 8636744]
8. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol.* 1999; 17:1736–1744. [PubMed: 10561210]
9. Thigpen T, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2001; 19:364–367. [PubMed: 11208827]

10. Rose PG, Blessing JA, Lewandowski GA, Creasman WT, Webster KD. A Phase II trial of prolonged oral etoposide (VP-16) as second-line therapy for advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1996; 63:101–104. [PubMed: 8898177]
11. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003; 88:277–281. [PubMed: 12648575]
12. Moore DH, Blessing JA, Dunton C, Buller RE, Reid G. Evaluation of dactinomycin in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 1999; 75:473–475. [PubMed: 10600310]
13. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2002; 20:2360–2364. [PubMed: 11981008]
14. Plaxe SC, Blessing JA, Hussein N, Webster KD, Rader JS, Dunton CJ. Evaluation of Pyrazoloacridine (PZA) (NSC #366140) in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2002; 84:241–244. [PubMed: 11812081]
15. Miller DS, Blessing JA, Lentz SS, Waggoner S. Evaluation of topotecan in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2002; 87:247–251. [PubMed: 12468321]
16. Fracasso PM, Blessing JA, Molpus KL, Adler LM, Sorosky JI, Rose PG. Phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006; 103:523–526. [PubMed: 16712905]
17. Schilder R, Blessing JA, Pearl ML, Rose PG. Evaluation of irifulven (MGI-114) in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. *Invest New Drugs.* 2004; 22:343–349. [PubMed: 15122083]
18. Grendys EC Jr. Blessing JA, Burger R, Hoffman J. A phase II evaluation of flavorpiridol as second-line chemotherapy of endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2005; 98:249–253. [PubMed: 15978659]
19. Garcia A, Blessing J, Nolte S, Mannel R. A phase II evaluation of weekly docetaxel (NSC #628503) in the treatment of recurrent or persistent endometrial carcinoma; A Gynecologic Oncology Group study. *Gynecol Oncol.* 2008; 111:2–26.
20. Miller DS, Blessing JA, Drake RD, Higgins R, McMeekin DS, Punecky LV, et al. A phase II evaluation of pemetrexed (ALIMTA, LY231514, IND#40061) in the treatment of recurrent or persistent endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol.* 2009; 115:443–446. [PubMed: 19804902]
21. Dizon DS, Blessing JA, McMeekin DS, Sharma SK, DiSilvestro P, Alvarez RD. Phase II trial of ixabepilone as second line treatment in advanced endometrial cancer: Gynecologic Oncology Group Trial 129-P. *J Clin Oncol.* 2009; 27:3104–3108. [PubMed: 19451430]
22. Tait DL, Blessing JA, Hoffman JS, Moore KN, Spirtos NM, Lachance JA, et al. A phase II study of gemcitabine (GEMZAR, LY188011) in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2011; 212:118–121. [PubMed: 21159366]
23. 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; 129:486–94. [PubMed: 23438670]
24. Leslie KK, Sill MW, Lankes HA, Fischer EG, Godwin AK, Gray H, et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. *Gynecol Oncol.* 2012; 127:345–350. [PubMed: 22885469]
25. Coleman RL, Sill MW, Thaker P, Bender DP, DeGeest K, Street D, et al. A phase II evaluation of AZD6244, a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2013; 130:e12–e13. Abstract.
26. McMeekin DS, Sill MW, Benbrook D, Darcy KM, Stearns-Kurosawa DJ, Eaton L, et al. A phase II trial of thalidomide in patients with persistent or recurrent endometrial cancer with translational

- research: a Gynecologic Oncology Group study. *Gynecol Oncol* . 2007; 105:508–516. [PubMed: 17306350]
27. 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]
 28. Coleman RL, Sill MW, Lankes HA, Nickles Fader AN, Finkler NJ, Hoffman JS, et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012; 127:538–43. [PubMed: 22922531]
 29. Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013; 129:22–27. [PubMed: 23262204]
 30. Powell MA, Sill MW, Goodfellow PJ, Benbrook DM, Lankes HA, Leslie KK, Jeske Y, et al. A phase II trial of brivanib, in recurrent or persistent endometrial carcinoma: an NRG Oncology/ Gynecologic Oncology Group study. *Gynecol Oncol*. 2014; 135:38–43. [PubMed: 25019571]
 31. Dizon DS, Sill MW, Schilder JM, McGonigle KF, Rahman Z, Miller DS, et al. A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. 2014; 135:441–445. [PubMed: 25312396]
 32. Makker V, Filiaci V, Chen L, Darus C, Kendrick JE, Sutton G, et al. Phase II evaluation of dalantercept, a soluble recombinant activin receptor-like kinase 1 (ALK1) receptor-fusion protein, for treatment of recurrent/persistent endometrial cancer: GOG 0229N. *Gynecol Oncol*. Apr 16.2015 epub ahead of print.
 33. Bender, D.; Sill, M.; Schilder, J.; Samuelson, M.; Rotmensch, J., et al. A phase II evaluation of cedirinib in the treatment of recurrent or persistent endometrial cancer: An NRG/GOG study. LBA 4.. SGO 2015 Annual Meeting; Chicago, IL. March 30, 2015;
 34. Talvensaaari-Mattila A, Soini Y, Santala M. VEGF and its receptors (flt-1 and KDR/flk-1) as prognostic indicators in endometrial carcinoma. *Tumour Biol*. 2005; 26:81–87. [PubMed: 15867479]
 35. Saito M, Sato Y, Watanabe J, Kuramoto H, Kaba S, Fukuda T. Angiogenic factors in normal endometrium and endometrial adenocarcinoma. *Pathol Int*. 2007; 57:140–147. [PubMed: 17295646]
 36. Yu Y, Varughese J, Brown LF, Mulliken JB, Bischoff J. Increased Tie2 expression, enhanced response to angiopoietin-1 and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells. *Am J Pathol*. 2001; 159:2271–2280. [PubMed: 11733376]
 37. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature*. 2000; 407:242–248. [PubMed: 11001067]
 38. Maisonpierre PC, Suri C, Jones PF, Bartunkova S, Wiegand SJ, Radziejewski C, et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. *Science*. 1997; 277:55–60. [PubMed: 9204896]
 39. Coxon A, Bready J, Min H, Kaufman S, Leal J, Yu D, et al. Context dependent role of angiopoietin 1 inhibition in the suppression of angiogenesis and tumor growth: implications for AMG 386, an angiopoietin ½ neutralizing peptibody. *Mol Cancer Ther*. 2010; 9:2641–2651. [PubMed: 20937592]
 40. AMG 386 investigator brochure.
 41. Herbst RS, Hong D. Chap I et al. safety, pharmacokinetics and antitumor activity of AMG 386 a selective angiopoietin inhibitor in adult patients with advanced solid tumors. *J Clin Oncol*. 2009; 27:3557–3565. [PubMed: 19546406]
 42. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, et al. Anti angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomized, multicentre, double blind, placebo controlled phase 3 trial. *Lancet Oncol*. 2014; 15:799–808. [PubMed: 24950985]

43. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45:228–247. [PubMed: 19097774]
44. Sill MW, Rubinstein L, Litwin S, Yothers G. A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials. *Clin Trials*. 2012; 9:385–95. [PubMed: 22811448]
45. Castonquay V, Lheureux S, Welch S, Mackay HJ, Hirte H, Fleming G, et al. A phase II trial of sunitinib in women with metastatic or recurrent endometrial carcinoma: a study of the princess Margaret, Chicago and California consortia. *Gynecol Oncol*. 2014; 134:274–280. [PubMed: 24882554]
46. Nimeiri HS, Oza AM, Morgan RJ, Huo D, Elit L, Knost JA, et al. Sorafenib in patients with advanced/recurrent uterine carcinoma or carcinosarcoma: a phase II trial of the University of Chicago, PMH and California Phase II consortia. *Gynecol Oncol*. 2010; 117:37–40.
47. Homesley HD, Meltzer NP, Nieves L, Vaccarello L, et al. A phase II trial of weekly 1-hour paclitaxel as second line therapy for endometrial and cervical cancer. *Int J Clin Oncol*. 2008; 12:62–65. [PubMed: 18307021]

RESEARCH HIGHLIGHTS

- Agents targeting angiogenesis have met with modest success in recurrent endometrial cancer
- Trebananib is a novel anti-angiogenesis agent targeting the Ang1 Ang2 to Tie 2 interface. This is distinct from VEGF directed therapy
- Trebananib did not meet pre-specified response endpoints in the single arm, phase 2 trial.

Endpoint	Estimate	90% Confidence Interval
Median PFS	1.97 months	1.77 – 2.10
Median OS	6.60 months	4.01 – 14.75

Figure 1.
Median progression free and overall survival for patients with recurrent/persistent endometrial cancer treated with trebananib.

Table 1

Patient Characteristics (n= 32)

Characteristic	Category	N (%)
Age Group	40-49	1 (3.1)
	50-59	6 (18.8)
	60-69	11 (34.4)
	70-79	14 (43.8)
Ethnicity	Hispanic	2 (6.3)
	Non-Hispanic	29 (90.6)
	Unknown	1 (3.1)
Race	White	29 (90.6)
	Black/African American	2 (6.3)
	American Indian/Alaskan	1 (3.1)
Performance Status	0	18 (56.3)
	1	14 (43.8)
Histology/Grade	Endometrioid, Grade 1	6 (18.8)
	Endometrioid, Grade 2	4 (12.5)
	Endometrioid, Grade 3	9 (28.1)
	Serous	10 (31.3)
	Mixed Epithelial	3 (9.4)
Prior Radiation	No	18 (56.3)
	Yes	14 (43.8)
Prior Chemotherapy	1 Prior Regimen	25 (78.1)
	2 Prior Regimens	7 (21.9)

Table 2

Adverse Events (n=32)

AE Category	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	%
Fatigue	10	11	9	2	0	0	69%
Anemia	15	15	2	0	0	0	53%
Constipation	16	10	6	0	0	0	50%
Hypertension	20	1	7	4	0	0	38%
Nausea	20	6	2	4	0	0	38%
Abdominal Pain	20	1	3	8	0	0	38%
Edema limbs	21	4	5	2	0	0	34%
Anorexia	22	6	3	1	0	0	31%
Peripheral Sensory Neuropathy	22	10	0	0	0	0	31%
Cough	24	7	1	0	0	0	25%
Diarrhea	24	6	2	0	0	0	25%
Hyperglycemia	24	6	2	0	0	0	25%
Hyponatremia	24	5	0	2	1	0	25%
Hypoalbuminemia	24	3	3	2	0	0	25%
Dyspnea	25	4	1	2	0	0	22%
Vomiting	25	2	3	2	0	0	22%
Ascites	27	0	2	3	0	0	16%
Bloating	28	1	3	0	0	0	13%
Lymphedema	28	1	1	2	0	0	13%
Thromboembolic event	28	0	2	2	0	0	13%
Localized Edema	29	3	0	0	0	0	9%

Table 3

Efficacy (n=32)

Characteristic	Category	N	% of Cases
RECIST Response	Partial Response	1	3.1
	Stable Disease	8	25
	Progressive Disease	20	62.5
	Indeterminate	3	9.4
PFS > 6 months	No	26	81.3
	Yes	6	18.8
EFS > 6 months	No	27	84.4
	Yes	5	15.6
Cycles of Treatment	1	7	21.9
	2	17	53.1
	3-5	1	3.1
	9+	5	15.6

Table 4

History of phase II trials evaluating anti-angiogenesis agents in recurrent/metastatic endometrial cancer completed through the Gynecologic Oncology Group

GOG Protocol	Agent	N	ORR (%)	Probability of PFS at 6 months	Median PFS (months)
GOG 229B ²⁶	Thalidomide	24	12	0.08	1.7
GOG 229E ²⁷	Bevacizumab	52	13.5	0.40	4.2
GOG 229F ²⁸	Aflibercept	44	6.8	.41	2.9
GOG 229G ²⁹	Bevacizumab+Temozolomide	49	24.5	.469	5.6
229J ³⁰	Brivanib	43	18.6	.302	3.3
229J ³³	Cediranib	53	12.5%	.333	
229K ³¹	Nintedanib	32	9.4	.219	3.3
229L	Trebananib	32	3.1	.19	1.97
229N ³²	Dalantercept	28	0	.11	2.1