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Efficacy and safety of tivozanib in recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer, an NCCN phase II trial

Mathew Cowan [a], Wendy M. Swetzig [a], Valery Adorno-Cruz [a], Mario J. Pineda [a,b], Nikki L. Neubauer [a], Emily Berry [a], John R. Lurain [a,b], Shohreh Shahabi [a,b], Deanna Taiym [b], Valerie Nelson [c], Kaitlyn Lucrezia O'Shea [d], Masha Kocherginsky [d], Daniela Matei [a,b,e,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[b] Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[c] Northwestern Medicine, Lake Forest Hospital, Lake Forest, IL, USA
[d] Division of Biostatistics, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[e] Jesse Brown VA Medical Center, Chicago, IL 60612, USA

HIGHLIGHTS

- Tivozanib is a potent vascular endothelial growth factor receptor tyrosine kinase inhibitor.
- Response rate to Tivozanib in platinum-resistant ovarian cancer is 16.7%; median progression-free survival is 4.1 months.
- The most common adverse events were fatigue and hypertension.

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ABSTRACT

Objective. Tivozanib is a potent selective pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor with a long half-life. This study assessed its activity in patients with recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer (OC).

Methods. This open-label phase II study used a Simon's two-stage design. Eligible patients had recurrent, platinum-resistant OC and measurable or detectable disease. There was no limit on the number of prior regimens. Treatment consisted of tivozanib 1.5 mg orally once daily for 21 days in a 28-day cycle. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity assessment.

Results. Thirty-one patients were enrolled, and 30 were treated. The median age was 59.5 years, and median number of prior regimens was 4 (range 1–9). Twenty-four patients were evaluable for response, and four (16.7%) achieved a partial response (PR; ORR = 16.7%). An additional fourteen (58.3%) patients had stable disease (SD). The clinical benefit rate (PR + SD) was 75.0%, and the median duration of objective response was 5.7 months. For all patients on trial, the median PFS was 4.1 months (95% confidence interval (CI): 1.7–5.8) and OS 8.6 months (95% CI: 5.4–12.5). There were no treatment-related deaths. Serious adverse events occurred in 13.3% of patients and included small intestinal perforation or obstruction and stroke. Grade 3–4 adverse events occurred in 60% of patients, including hypertension (26.7%) and fatigue (10%).

Conclusions. Tivozanib is effective in patients with recurrent OC, with moderate toxicity and no treatment-related deaths, supporting its further development.

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1. Introduction

Ovarian cancer (OC) is the fifth most common cancer in women and remains the most fatal gynecologic malignancy [1]. After initial responses to surgery and platinum-based chemotherapy, most patients with advanced disease eventually recur and tumors become resistant to platinum-based chemotherapy [2]. A bevy of additional cytotoxic

* Corresponding author at: 303 East Superior Street, Lurie 4-107, Chicago, Illinois 60611, USA.
E-mail address: Daniela.matei@northwestern.edu (D. Matei).

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chemotherapeutic agents have proven active in this setting, although response rates and durations of responses are typically modest [3,4]. In an effort to improve clinical outcomes, new classes of drugs targeting biological pathways known to be important in OC progression are continuously being tested, including angiogenesis inhibitors, immunotherapeutic agents, PARP inhibitors, receptor tyrosine kinase inhibitors, and others [5]. Such new inhibitors are being investigated as single agents or in combination with traditional cytotoxic agents [1,6,7].

Interrupting tumor neovascularization by targeting the vascular endothelial growth factor (VEGF) receptor-ligand interaction arrests an important early step in tumor growth. Several agents that target angiogenesis have been developed, tested, and many have gained approval for the treatment of a variety of solid tumors. Anti-VEGF therapy has direct effects on blood vessels by stopping the sprouting of new vessels, destroying existent vessels and leading to normalization of abnormally tortuous and fenestrated vessels [8,9]. Additionally, in certain tumors, like OC, anti-VEGF therapy has direct effects on tumor cells, inhibiting their proliferation [10]. The effects of anti-VEGF agents on blood vessels lead to increasing hypoxia and nutrient deprivation inside tumors, driving cancer cells to apoptosis [11]. Phase II clinical studies demonstrated that bevacizumab, a monoclonal antibody which binds the ligand VEGF-A, has high activity as single agent in recurrent OC [12,13]. Addition of bevacizumab to upfront or second line chemotherapy in OC prolonged progression-free survival (GOG218, ICON4 and OCEAN trials) and regimens incorporating anti-VEGF therapy have become new standard combinations for OC [14–17]. Bevacizumab has also been shown to be have durable activity in recurrent OC as both monotherapy or maintenance therapy [12,15,16]. Other compounds which target the tyrosine kinase domain of the three VEGF receptors (VEGFR-1, −2, −3), such as pazopanib, sorafenib, cabozantinib and tivozanib have also shown activity in OC [18–21], consistent with broad effects of this pathway's blockade.

Tivozanib is a highly-potent and selective inhibitor of all three VEGFRs, and has been shown to block VEGF-induced endothelial cell migration, differentiation and survival, affecting both blood and lymph vessels. Decreased tumor vascularity and growth potential has been demonstrated in various mouse xenograft tumor models, including in OC models [18,22]. Phase I/II trials in patients with renal cell carcinoma (RCC), breast, colorectal and OC tested the safety and activity of oral tivozanib, reporting a tolerable toxicity profile as well as a promising and durable response rate [23,24]. This led to further development of the agent in solid tumors, and particularly in renal cancer, where tivozanib received approval in the European Union for standard treatment. Given the significance of the VEGF-VEGFR pathway to OC progression and the high potency of this kinase inhibitor in other solid tumors where angiogenesis plays a significant role, the single agent activity of tivozanib was evaluated here in a hard-to-treat patient population with recurrent OC.

In this multi-institutional phase II study, we investigate the use of tivozanib 1.5 mg orally for 21 days in a 28-day cycle for treatment of platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer ("ovarian cancer"; OC). The primary endpoint of the trial was assessment of the overall response rate (ORR) and the secondary endpoints included assessment of the response duration, overall survival (OS) and toxicity.

2. Materials and methods

2.1. Patient eligibility

Eligible patients were women with recurrent or persistent platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. Platinum-resistance was defined as disease recurrence within six months of completing platinum-based adjuvant therapy. Patients with either measurable or detectable disease were eligible for enrollment. Measurable disease was defined as presence of at least one "target lesion" as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Those with no measurable disease must have had cancer antigen 125 (CA-125) level greater than two times the upper limit of normal and detectable disease such as either ascites/pleural effusion or hypermetabolic lesions on positron emission tomography (PET) scan. Patients must have had at least one prior taxane and platinum-based chemotherapy regimen, but there was no maximum number of prior treatments allowed. Patients who had received investigational or licensed drugs targeting VEGF or VEGF receptors/pathways for the treatment of recurrent cancer were not eligible; however, use of bevacizumab in the adjuvant setting was allowed. Patients must have recovered from recent surgery, radiation or chemotherapy and be free of infection. Key exclusion criteria included age < 18, Eastern Cooperative Oncology Group (ECOG) performance status >2, previous treatment with tivozanib, central nervous system metastases, hemoglobin <9.0 g/dL, absolute neutrophil count (ANC) < 1500/mL, platelets <100,000/mL, abnormal liver or kidney function, or prior gastrointestinal condition with increased risk of bowel perforation. Patients with major bleeding episodes or venous thromboembolism in the six months prior to enrollment were also excluded. The study was approved by the Institutional Review Board at Northwestern University and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and all applicable local regulatory requirements and laws. All patients provided written informed consent.

2.2. Study design and treatment

This was an open-label phase II trial of tivozanib hydrochloride administered 1.5 mg orally on days 1–21 days in a 28-day cycle. Concomitant administration of chemotherapy or other systemic treatment for OC, inhibitors of CYP3A4, or St John's Wart was prohibited. Dose interruption for <2 weeks was allowed in the case of clinically-significant Grade 3/4 adverse events (AE), including hematologic toxicity with ANC of <1500/mL or platelets of <100,000/mL. Patients with hypertension were treated medically before dose reduction or discontinuation. If hypertension was not adequately controlled by pharmacologic intervention, it was managed in a similar manner as other toxicities with drug interruption, dose reduction or discontinuation. If the toxicities resolved in <1 week, the same treatment cycle was continued, if the interruption was ≥1 week, a new cycle was initiated. Dose reduction to 1.0 mg per day was allowed in patients who required interruption and/or who were not able to re-escalate dose during the study enrollment. If the toxicities did not resolve to baseline within 2 weeks, the treatment was discontinued. Treatment was discontinued at disease progression, initiation of a subsequent cancer treatment or withdrawal from the study for any reason. After treatment discontinuation, patients were followed every 3 months for 2 years and then every 6 months for 3 years.

2.3. Toxicity assessment

At baseline, physical examination, 12-lead electrocardiogram (EKG), complete blood count (CBC), serum chemistries, urine dipstick (for protein), and coagulation profile were obtained. Physical examination, EKG, CBC, and chemistries were obtained before each cycle and urine dipstick was checked before every other cycle. Adverse events (AEs) were evaluated weekly and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Tumor response was assessed every 8 weeks, according to RECIST version 1.1.

2.4. Response assessment

The primary outcome in this trial was ORR as determined by physical examination, serum CA-125 levels and/or measurement of "target lesions" by RECIST. Patients with measurable disease were assessed by RECIST criteria, with scans being repeated every two cycles. Patients

with detectable disease were assessed with CA125 levels measured at each cycle. ORR was defined as the sum of complete responses (CRs; e.g., disappearance of all target lesions, or normalization of CA-125) and partial responses (PRs, e.g., >30% decrease in the sum or the diameters of the target lesions, or > 50% decrease in CA-125). CA125 response was defined as at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients were evaluated according to CA 125 only if they had a pretreatment sample at least twice the upper limit of normal. Secondary outcomes included assessment of stable disease (SD), clinical benefit rate (CBR; defined as ORR plus SD > 4 months), duration of progression-free survival (PFS) and overall survival (OS).

2.5. Statistical design

This phase II study used Simon's two stage design to test the null hypothesis that ORR ≤ 5% vs. the alternative hypothesis ORR ≥ 20% with 80% power and one-sided $\alpha = 0.05$ Type I error. Ten patients were to be enrolled during the first stage. If 1 or more responses (CR or PR) were observed, an additional 20 patients would be enrolled in the second stage, and the null hypothesis would be rejected if 4 or more responses are observed among all 30 patients. On 10/12/16 the Northwestern Data Safety and Monitoring Committee reviewed the first 12 evaluable patients for an interim analysis and approved the study continuation. Duration of response, PFS, and OS were estimated using the Kaplan-Meier method. IHC staining scores were compared between groups using the Wilcoxon rank sum test. Analyses were performed using R statistical software [25].

2.6. Immunohistochemistry (IHC)

Archival paraffin embedded tissue was obtained from 17 consenting patients enrolled on the trial. Sections were heated at 56 °C for 30 min followed by deparaffinization and hydration. Antigen retrieval was performed using 0.01 M citrate buffer, pH 6. Immunostaining for VEGFR1 (R&D, AF321), VEGFR2 (R&D, MAB3571) and VEGFR3 (Invitrogen, MA5–11168) were performed overnight in 1% bovine serum albumin (BSA). Hydrogen peroxidase block was performed using 3% hydrogen peroxide for 30 min. Incubation with labelled streptavidin biotin (DAKO LSAB2 system cat#K0675) followed by 3,3′-diaminobenzidin (DAB) was performed for detection. Slides were counterstained with hematoxylin and cover-slipped with aqueous solution. Slides were scored based on intensity of staining on a 0 to 3+ scale, noting proportion (%) of staining tumor cells and the H score was calculated as the intensity X proportion of cells staining.

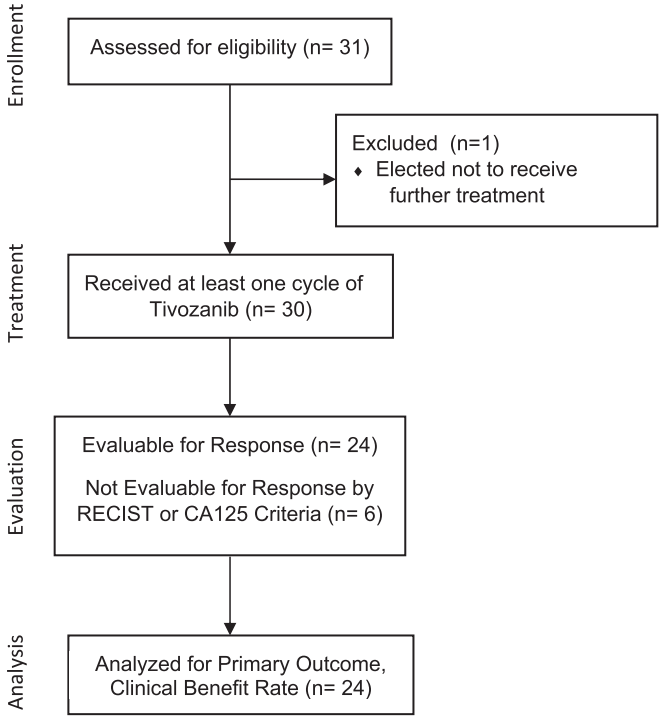

Fig. 1. Patient Selection.
Modified CONSORT diagram for enrollment and analysis of patients in a single-arm trial.

3. Results

3.1. Patient characteristics

A total of 31 eligible patients with platinum-resistant ovarian, fallopian tube or primary peritoneal cancer were enrolled between June 2013 and September 2018. One patient elected not to receive treatment after initial enrollment and thus was not evaluable (Fig. 1). For the 30 patients treated on this protocol, median age was 59.5 years (range 44–93). Most patients had ovarian cancer ($n = 19$, 63.3%), stage III at diagnosis (n = 19, 63.3%), serous histology ($n = 23$, 76.7%) and high-grade features ($n = 28$, 93.3%). The median number of prior systemic therapies was 4 (range 1–9 therapies) and median number of prior platinum therapies was 2 (range 1–6 therapies). Seven patients had previously received bevacizumab and 26 had RECIST measurable disease (Table 1).

Table 1
Patient characteristics.

Overall ($N = 30$)	
Age at Registration in Years	
Median (Range)	59.5 (44.0–93.0)
Race	
Black	2 (6.7)
White	28 (93.3)
Ethnicity	
Hispanic or Latino	2 (6.7)
Non-Hispanic	28 (93.3)
Primary Tumor Site	
Fallopian Tube	10 (33.3)
Ovarian	19 (63.3)
Primary Peritoneal	1 (3.3)
FIGO Stage at Diagnosis	
I	2 (6.7)
II	4 (13.3)
III	19 (63.3)
IV	5 (16.7)
Tumor Type	
High-grade serous	21 (70.0)
Low-grade serous	2 (6.7)
High-grade, other histology	7 (23.3)
Tumor Histology	
Serous	23 (76.7)
Mixed Epithelial	2 (6.7)
Clear Cell/Mucinous	4 (13.3)
Other	1 (3.3)
Baseline lesion status	
Measurable	26 (86.7)
Evaluable	4 (13.3)
Received Prior Systemic Therapies	
No	1 (3.3)
Yes	29 (96.7)
Number received per patient (Median (Range))	4 (0–9)
Received Prior Platinum Therapies	
No	2 (6.7)
Yes	28 (93.3)
Number received per patient (Median (Range))	2 (0–6)
Received Prior Bevacizumab	
No	23 (76.7)
Yes	7 (23.3)

Data are n (%) unless otherwise noted.

Table 2
Summary of Efficacy for all patients and patients evaluable for response.

All patients	(n = 30)
Progression-Free Survival (months)	
Median (95% CI)	4.1 (1.7–5.8)
Overall Survival (months)	
Medial (95% CI)	8.6 (5.4–12.5)
Best Response	
Complete Response	0 (0.0)
Partial Response	4 (13.3)
Stable Disease	14 (46.7)
Progressive Disease	6 (20.0)
Not evaluable	6 (20.0)
Patients Evaluable for Response	**(*n* = 24)**
Objective Response Rate	4 (16.7)
Duration of Objective Response (months)	
Median (95% CI)	5.7 (3.7 – NA)
Clinical Benefit Rate	18 (75.0)

CI = Confidence Interval, NA = Not Applicable.
All data are n (%) unless otherwise noted.

3.2. Clinical activity

Six patients were not evaluable for response (Table 2). For the 24 patients evaluable for response, the ORR was 16.7% (95% CI 4.7–37.4%); four patients had confirmed PR, but no CR were recorded. In patients who achieved PR, the median duration of response was 5.7 months. Another 14 patients (58.3%) had SD as best disease response, leading to a total CBR of 75.0% (95% CI 4.7–37.4%; Table 2). In the overall population, the median PFS was 4.1 months (95% CI: 1.7–5.8) and a 6-month PFS rate of 26.7% (95% CI: 14.7% - 48.3%). The median OS was 8.6 months (95% CI: 5.39–12.5 months; Fig. 2). All four patients with PRs had measurable disease. Two had high-grade serous and two had low-grade serous tumors, and were heavily pre-treated, with a median of 3.5 (range 1–5) prior systemic therapies, and 2 (range 1–3) prior platinum therapies. Among the patients with detectable disease ($n = 4$) there were no responses by CA-125 criteria. Of the 30 enrolled patients, 15 were assessable by CA125 response criteria. Of those, there were 4 responses, for a CA125 RR of 26.7%.

3.3. Toxicity

There were no treatment-related deaths. Grade 3/4 AEs occurred in 18 patients (60.0%), most commonly hypertension ($n = 8$, 26.7%) and fatigue ($n = 3$, 10.0%). Grade 1/2 AEs were more common ($n = 29$, 96.7%), with fatigue ($n = 19$, 63.3%), hypertension ($n = 13$, 43.3%), anorexia ($n = 12$, 40%), diarrhea (n = 12, 40%), arthralgia ($n = 11$, 37%) and weight loss ($n = 10$, 33%) being most frequent (Table 3). Serious adverse events (SAEs) related to tivozanib included small bowel perforation (Grade 1/2, n = 1; Grade 3/4, n = 1), small bowel obstruction (Grade 3/4, n = 1), and stroke (Grade 3/4, n = 1; Table 3). Additional intestinal SAEs thought to be unrelated to tivozanib included small bowel obstruction (Grade 3/4, $n = 3$), colonic obstruction (Grade 3/4, n = 1), nausea, vomiting, and constipation (Grade 1/2, n = 1 each; Supplemental Table 1).

3.4. Dose interruptions and reductions

There were 156 cycles attempted during the trial, with a median of 2 cycles per patient (range 1–32), with 12 patients receiving >2 cycles. A total of 39 dose interruptions occurred in 16 patients (53.3%, median = 1.0 interruptions per patient), and 7 dose reductions occurred in 7 patients (23.3%). Of the 12 patients who received >2 cycles, 5 (41.7%) required dose reductions at some point during the trial. The agent was discontinued in five (16.7%) patients for toxicity, and 1 (3.3%) patient withdrew consent before the second cycle.

3.5. Immunohistochemistry

Of the three VEGF receptors, VEGFR2 was highly expressed (H score 2–3) in 76.5% of the patients (Fig. 3). In contrast, 23.5% and 50% of patients displayed high expression of VEGFR1 and VEGFR3, respectively (Supplemental Table 2). No association between expression of either receptor with clinical response or PFS were found.

4. Discussion

Tivozanib is an active agent in the treatment of recurrent or platinum-resistant OC, with a 16.7% ORR and 75.0% CBR. The study achieved the required number of responses based on Simon's two-stage design. Overall median PFS was 4.1 months and median OS was 8.6 months, but in those patients evaluable for response, the median PFS was 5.7 months. The drug regimen was fairly well tolerated, with moderate toxicity and no treatment-related deaths.

The dosing regimen used in this trial was derived from a phase I pharmacokinetic and safety trial [26]. In that study, dosing was deescalated from 2.0 mg daily due to dose-limiting Grade 3/4 AEs hypertension, proteinuria and ataxia. The most common Grade 3/4 AEs

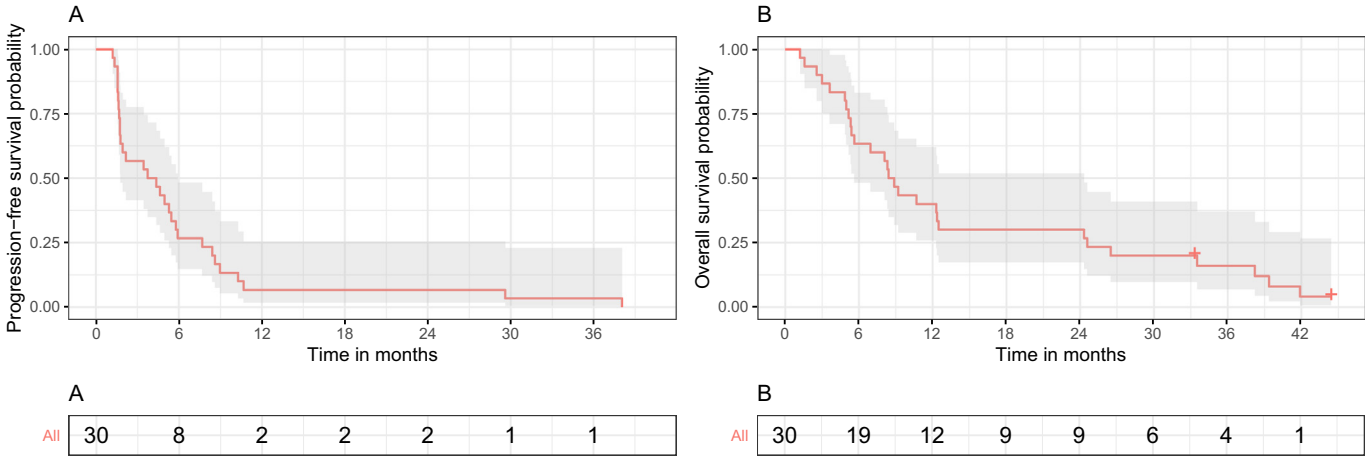

Fig. 2. Progression-free and Overall Survival.
Median progression free survival is 4.1 months (95% CI 1.74–5.78). Two patients had prolonged progression-free survival. Median overall survival is 8.6 months (95% CI 5.39–12.5). CI = confidence interval.

Table 3
Adverse and Serious Adverse Events Related to Tivozanib.

Adverse Events			
Event	Grade 1–2	Grade 3–4	Total
Fatigue	19 (63.3)	3 (10.0)	22 (73.3)
Hypertension	13 (43.3)	8 (26.7)	21 (70.0)
Anorexia	12 (40.0)	–	12 (40.0)
Diarrhea	12 (40.0)	–	12 (40.0)
Arthralgia	11 (36.7)	–	11 (36.7)
Weight loss	10 (33.3)	–	10 (33.3)
Nausea	7 (23.3)	1 (3.3)	8 (26.7)
Headache	8 (26.7)	–	8 (26.7)
Hoarseness	8 (26.7)	–	8 (26.7)
Dyspnea	6 (20.0)	–	6 (20.0)
Vomiting	6 (20.0)	–	6 (20.0)
Hyponatremia	4 (13.3)	2 (6.7)	6 (20.0)
Bloating	5 (16.7)	–	5 (16.7)
Myalgia	5 (16.7)	–	5 (16.7)
Serious Adverse Events			
Event	Grade 1–2	Grade 3–4	Total
Small intestine perforation	1 (3.3)	1 (3.3)	2 (6.6)
Small intestine obstruction	–	1 (3.3)	1 (3.3)
Stroke	–	1 (3.3)	1 (3.3)

at the 1.5 mg daily dose were hypertension (62%) and fatigue (6%). This dosing was adopted for further phase I and II studies in solid tumors, RCC, glioblastoma, and in combination with taxanes for breast cancer [23,24,27–29]. Grade 3/4 AEs in these trials included hypertension (10–22%), diarrhea (2–11.1%), fatigue (3–16.7%), proteinuria (22%). There was a single colonic perforation among the 10 patients in the glioblastoma trial. We experienced similar rates of Grade 3/4 hypertension (26.7%), fatigue (10%) as the most common severe toxicities. One patient developed a stroke, associated with hypertension. Additionally, we observed intestinal perforation, obstruction and fistula formation in several patients (13.3%), in line with expected toxicities of anti-VEGF strategies in OC patient populations.

Tivozanib had shown promising early results in several studies of RCC, a tumor in which near-universal pathogenic mutations induce a state of upregulated VEGF expression. A Japanese phase Ib study of advanced solid tumors included 4 patients with RCC who were treated with 1.5 mg per day of tivozanib [23]. Of those patients, 75% ($n = 3$) achieved SD for over one year. A phase II study of tivozanib in RCC achieved 24% ORR and median PFS was 11.7 months [24]. Subsequent phase III trials demonstrated the pan-VEGR blockade of tivozanib improved PFS, ORR and response duration, with similar OS when compared to sorafenib, the standard VEGF tyrosine kinase inhibitor treatment in RCC [30–32].

VEGF expression seems to be an important factor in ovarian carcinoma pathogenesis as well, with VEGF having been demonstrated to facilitate tumor migration and invasion, and promote tumor growth [33,34]. High level of VEGF expression is a negative prognostic factor in OC, and metastatic implants seem to have higher expression than their matched primary tumors [33,35–37]. Treatment of OC with the VEGF-targeting bevacizumab has been thoroughly investigated. A phase II study of single-agent bevacizumab with similar patient population as our trial, those with recurrent or persistent OC, showed a median PFS of 4.7 months and median OS of 17 months [12]. Of the 13 patients (21.0%) who had PR

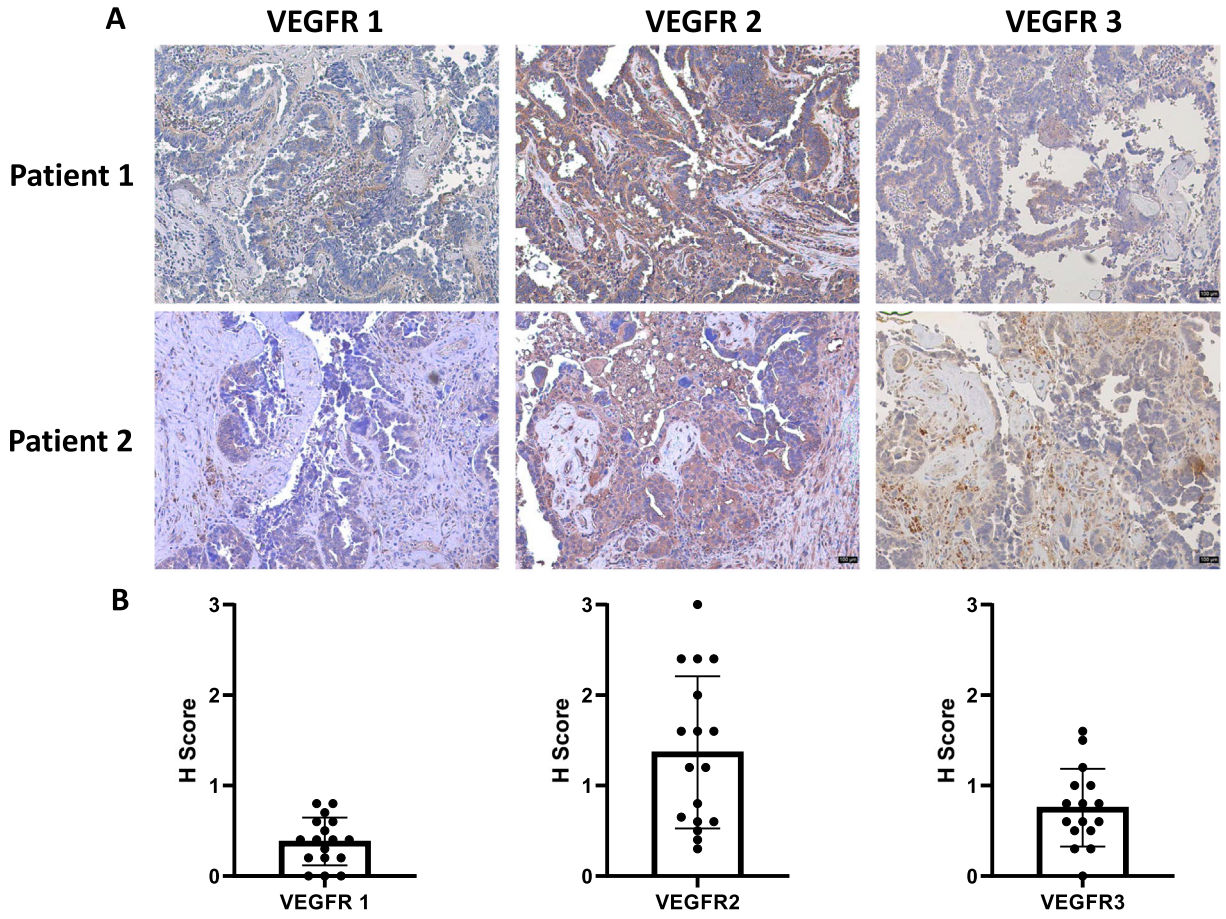

Fig. 3. Expression of vascular endothelial growth factor receptors (VEGFR).
A) Representative immunohistochemistry staining for VEGFR in two patients. B) Distribution of H-score for the expression of VEGFR shows the most intense staining in VEGFR2 ($n = 17$).

or CR, 11 remained progression-free at 6 months. Including patients who had stable disease ($n = 32$, 51.6%), 40.3% of patients treated on that study continued without progression at 6 months. This cohort experienced grade 3 hypertension in 9.7%, gastrointestinal events in 6.5% (with no perforations or fistulae), and grade 4 proteinuria in one patient (1.6%). Based on this study and further phase III trials, bevacizumab has become a mainstay agent in the treatment of OC in the upfront and recurrent settings [14–17]. Interestingly, a correlation between expression of VEGF or its receptors to response to anti-angiogenic agents has not been established in previous studies, as well as in this trial.

Sorafenib, an approved tyrosine kinase inhibitor for treatment of RCC, has also been studied in recurrent OC [21]. In OC, the CBR was 37.3%, with most responding patients achieving stable disease. However, the median PFS was only 2.1 months, but notably, the median duration of response was over 6 months and 5.1% of patients remained progression-free at the median follow-up of 23.6 months. GOG-254 tested sunitinib in recurrent clear cell OC, showing modest activity with a 20.0% CBR, but most of the responding patients obtained a PFS exceeding six months [38]. Likewise, pazopanib induced an ORR of 18% in patients with recurrent and low volume OC [39] and maintenance pazopanib after first line chemotherapy was shown to prolong PFS in a phase III trial [40]. Thus, compared to the other tyrosine kinase inhibitors tested in OC, but in less refractory settings, tivozanib has at least similar levels of activity. The current study targeted a more heavily pre-treated patient population and demonstrated moderate level of activity for the agent, thus placing tivozanib as a preferable agent for this setting. Whether tyrosine kinase inhibitors have a place in the management of OC, given the high level of activity and better tolerated toxicity profile of bevacizumab remains an open question in the field.

Based on the results of this study, we propose that tivozanib could have a place in the armamentarium of single-agent treatment strategies for platinum-resistant OC. As response rates to standard treatments in the setting of platinum-resistant OC range in single digits [3], innovation in treatment is desperately needed. Development of mechanistically synergistic drug combinations is a possible way to achieve this goal with the currently-available agents. For example, the addition of bevacizumab to standard single-agent chemotherapy showed an improvement in ORR, PFS and OS [14]. Response rates to VEGF pathway-directed strategies, such as tivozanib, could further be improved by identifying patients whose tumors would be particularly susceptible to angiogenesis inhibition.

Author contribution

Conceptualization, project administration: DM, NLN, MJP, Investigation: DM, JRL, MJP, EB, SS, NLN, VN; data curation and formal analysis: WMS, VAC, DT, KLO, MK; Writing – Original Draft: MC, DM; Writing – Review & Editing: All authors.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.08.005.

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