Efficacy and Safety of Tivozanib in Recurrent, Platinum-Resistant Ovarian, Fallopian Tube or Primary Peritoneal Cancer

W.M. Swetzig,[1] John R. Lurain,[1] Emily Berry,[1] Mario J. Pineda,[1] Shohreh Shahabi,[1] LaToya Perry,[2] Nikki L. Neubauer,[1] Wilberto Nieves-Neira,[1] Julian C. Schink,[1] Alissa Schiller,[3] Karen Novak,[3] Nancy J. Anderson,[3] Kirsten B. Burdett,[1] Anna E. Strohl,[1] Masha Kocherginsky,[1] Borko Jovanovic,[1] Daniela Matei[1]

[1] Northwestern University Feinberg School of Medicine, Chicago, IL; [2] Northwestern Medicine Regional Medical Group, Warrenville, IL; [3] Northwestern Medical Group, Chicago, IL

ABSTRACT

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

Methods:
This open-label phase II study used a Simon's two-stage design. Eligible patients had recurrent, platinum-resistant OC, FTC or PPC; ECOG PS of 0-1; normal end organ function; 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 (3 weeks on/1 week off). The primary endpoint was response rate. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity assessment. If 1 partial response (PR) was observed in stage I [n = 12], enrollment proceeded to stage II. The null hypothesis was rejected for ≥ 4 responses in 30 patients.

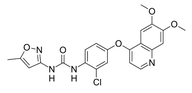
Results:
Thirty-one patients were enrolled, and 30 were treated. Nineteen had OC [63.33%], 10 FTC [33.33%] and 1 PPC [3.33%]. Twenty-six had measurable [86.67%] and 4 detectable disease [13.37%]. The median age was 60, and median number of prior regimens was 4 [range 1-9]. Four PRs [13.33%] were recorded. Twelve patients had stable disease (SD) [40%]. The clinical benefit rate (PR + SD) was 53.33%. Seven patients [23.33%] survived progression-free for > 6 mos. One patient continued treatment for > 2 yrs. The median PFS was 4 months [range 1-25] and median OS was 8 months [range 1-39]. There were no treatment-related deaths. Grade 3-4 related toxicities were hypertension [8], fatigue [3], fistula [2], hyponatremia [2], intestinal perforation, obstruction, stroke, proteinuria, hypomagnesemia, hypoalbuminemia, portal hypertension, nausea and anemia [1 each]. Frequent grade 1-2 related toxicities included fatigue [19], hypertension [13], anorexia [12], arthralgia [11], diarrhea [11], weight loss [10], hoarseness [8], headache [8] and nausea [7]. Exploratory analyses in tumor samples are ongoing.

Conclusions:
Tivozanib is active in patients with recurrent OC, FTC or PPC, without substantial toxicity, supporting its further development.

BACKGROUND

Tivozanib & Anti-Angiogenic Therapy in Ovarian Cancer

Tivozanib Structure

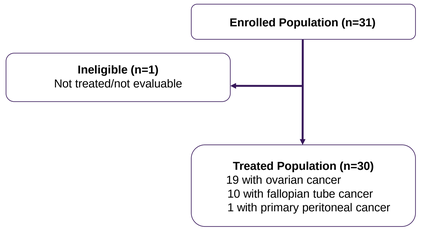


- Vascular Endothelial Growth Factor Receptor (VEGFR) tyrosine kinases play a key role in tumor angiogenesis and are frequently overexpressed in a variety of cancers, including OC.
- Anti-angiogenic agents, such as anti-VEGF mAbs and multi-receptor TKIs, are attractive therapeutic strategies for OC. The mAb bevacizumab (Avastin, Genentech Inc.) is FDA-approved in combination with chemotherapy for OC, FTC, or PPC in the recurrent, platinum-resistant and -sensitive settings. Other VEGFR inhibitors have been tested, but have not yet received approval status for gynecologic malignancies.
- Tivozanib is an orally bioavailable, potent, selective, long half-life inhibitor of VEGFR 1, 2, and 3, designed to optimize pan-VEGF blockade while minimizing off-target toxicities. It exhibits antineoplastic activity by inhibiting endothelial cell migration/proliferation and tumor angiogenesis, amongst additional mechanisms.
- Tivozanib has been approved for the treatment of adult patients with advanced renal cell carcinoma in the European Union, Norway, and Iceland. In North America, it is being studied in renal cell, hepatocellular, colorectal, and breast cancers.
- The present phase II study investigates the use of tivozanib in recurrent, platinum-resistant OC, FTC, and PPC.

METHODS

Study Overview

- **Design:**
  Open- label, phase II trial, using Simon's two-stage design.
- **Key Eligibility:**
  - Recurrent or persistent, platinum-resistant OC, FTC, or PPC
  - ECOG PS 0-1
  - Normal end organ function
  - Either RECIST 1.1 measurable disease or detectable disease. Detectible disease is defined as non-measurable disease of ascites or pleural effusions in the setting of elevated CA-125 (2x ULN).
- **Treatment Regimen:**
  Tivozanib 1.5 mg, PO, QD, 3 weeks on, 1 week off (1 cycle = 4 weeks) until progressive disease, unacceptable toxicity, withdrawal, or death.
- **Enrollment:**
  Thirty-one patients with platinum-resistant OC, FTC, or PPC were enrolled at Northwestern University/Medical Group and Northwestern Medicine Regional Medical Group in Illinois between 2013 and 2018, and 30 were treated with tivozanib.
- **Interim Analysis:**
  Stage I interim analysis (n=12 subjects) was conducted in October of 2016, and efficacy parameters were met with ≥ 1 partial or complete response (PR or CR) in Stage I. The study then proceeded to Stage II.
- **Statistics and Toxicity Analysis:**
  - Objective response rate (ORR) was calculated as the number of complete responses (CRs) and partial responses (PRs) according to RECIST 1.1 criteria.
  - The Kaplan-Meier method was utilized to estimate the median and overall distribution of progression free survival (PFS) and overall survival (OS).
  - Toxicity was evaluated per NCI-CTCAE v4.03 and was summarized by counts and frequencies.



OBJECTIVES

- **Primary Endpoint:**
  - **Objective response rate (ORR)**

  ORR is defined as the number of CRs and PRs per RECIST 1.1.
- **Secondary Endpoints:**
  - **Progression free survival (PFS)**

  Progression is defined as RECIST 1.1 progression, clinical progression, and/or CA-125 biomarker progression.

  - **Overall Survival (OS)**
  - **Toxicity assessment** according to NCI-CTCAE v4.03

RESULTS

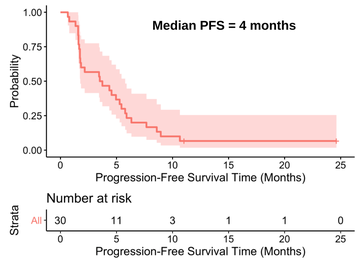
Patient Characteristics

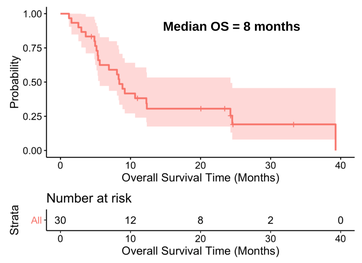
CHARACTERISTIC	FREQUENCY (n=30) [%]
Sex	
Female	30 [100.00%]
Male	0 [0.00%]
Race	
White	29 [96.67%]
Black	1 [3.33%]
Ethnicity	
Non-Hispanic/Latino	28 [93.33%]
Hispanic or Latino	2 [6.67%]
Tumor Type	
Ovarian	19 [63.33%]
Fallopian Tube	10 [33.33%]
Primary Peritoneal	1 [3.33%]
FIGO Tumor Stage	
I	2 [6.67%]
II	4 [13.33%]
III	19 [63.33%]
IV	5 [16.67%]
Tumor Grade	
High Grade and Grade 3	28 [93.33%]
Low Grade, Grade 1, and Grade 2	2 [6.67%]
Tumor Histology	
Serous	23 [76.67%]
Clear Cell/Mucinous	4 [13.33%]
Mixed Epithelial	2 [6.67%]
Other	1 [3.33%]
Disease Measurability Status	
Measurable Disease	26 [86.67%]
Evaluable Disease	4 [13.33%]
CHARACTERISTIC	**MEDIAN [RANGE]**
Age	60 [44-93]
Number of Prior Systemic Therapies	4 [1-9]
Number of Prior Platinum Therapies	2 [1-6]

Efficacy

Stage I efficacy parameters were met, and the study proceeded to stage II.

PROGRESSION & SURVIVAL OUTCOMES	MEDIAN (months) [RANGE]
Median Progression Free Survival (PFS)	4 [1-25]
Median Overall Survival (OS)	8 [1-39]
RESPONSE RATES	**FREQUENCY (n=30) [%]**
Objective Response Rate	4 [13.33%]
Clinical Benefit Rate (CBR; CR + PR + SD)	16 [53.33%]
6 Month PFS Rate	7 [23.33%]
SUBJECTS' BEST RESPONSES	**FREQUENCY (n=30) [%]**
Complete Response (CR)	0 [0.00%]
Partial Response (PR)	4 [13.00%]
Stable Disease (SD)	12 [40.00%]
Progressive Disease (PD)	11 [36.67%]
Not Evaluable (NE)	3 [10.00%]





RESULTS

Toxicity

Toxicity was assessed according to NCI-CTCAE v4.03.

AE Analysis

MOST FREQUENT TIVOZANIB-RELATED AEs (Highest Grade Per Subject)	FREQUENCY (PER n=30 SUBJECTS) [%]
Event	**Grade 1-2**
Fatigue	19 [63.33%]
Hypertension	13 [43.33%]
Anorexia	12 [40.00%]
Diarrhea	11 [36.667%]
Arthralgia	11 [36.667%]
Weight loss	10 [33.33%]
Headache	8 [26.667%]
Hoarseness	8 [26.667%]
Nausea	7 [23.33%]
Vomiting	6 [20.00%]
Event	**Grade 3-4**
Hypertension	8 [26.667%]
Fatigue	3 [10.00%]
Colonic fistula	2 [6.667%]
Hyponatremia	2 [6.667%]
Anemia	1 [3.33%]
Hypoalbuminemia	1 [3.33%]
Hypomagnesemia	1 [3.33%]
Nausea	1 [3.33%]
Portal hypertension	1 [3.33%]
Proteinuria	1 [3.33%]
Small intestinal obstruction	1 [3.33%]
Small intestinal perforation	1 [3.33%]
Stroke	1 [3.33%]
Event	**Grade 5**
None experienced	N/A

SAE Analysis

ALL SAEs (Highest Grade Per Subject)	FREQUENCY (PER n=30 SUBJECTS) [%]			
	Grade 1-2	Grade 3-4	Grade 5	All Grades
SAEs Related to Tivozanib	1 [3.33%]	3 [10.00%]	0 [0.00%]	4 [13.33%]
Small intestinal perforation	1 [3.33%]	1 [3.33%]		
Small intestinal obstruction		1 [3.33%]		
Stroke		1 [3.33%]		
SAEs Unrelated to Tivozanib	7 [23.33%]	5 [16.67%]	0 [0.00%]	12 [40.00%]
Ileal obstruction		2 [6.67%]		
Small intestinal obstruction		1 [3.33%]		
Colonic obstruction		1 [3.33%]		
Ascites	1 [3.33%]			
Tumor pain		1 [3.33%]		
Abdominal pain	1 [3.33%]			
Constipation	1 [3.33%]			
Nausea	1 [3.33%]			
Vomiting	1 [3.33%]			
Sinus tachycardia	1 [3.33%]			
Non-cardiac chest pain	1 [3.33%]			
Number of Subjects Experiencing an SAE	5 [16.67%]	8 [26.67%]	0 [0.00%]	12 [40.00%]

CONCLUSIONS

- Tivozanib is active in patients with recurrent, platinum-resistant OC, FTC or PPC.
- Tivozanib induces mild to moderate toxicity, mostly hypertension, fatigue and gastrointestinal events. Rare events include SB perforation, obstruction, stroke.
- These findings support further development of Tivozanib for the treatment of ovarian cancer.

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