A multi-centre Phase II study of bevacizumab (B) and temsirolimus (T) in women with recurrent epithelial ovarian cancer (OC): A study of the Mayo, Chicago, California, New York, Southeast, and Princess Margaret Phase II Consortia.

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Abstract

Background: Anti-angiogenic therapy is active in OC; the combination of VEGF and mTOR inhibitors is hypothesized to further improve activity. This report is the OC cohort of a multi-histology phase II study assessing the activity and toxicity of B/T. **Methods:** Patients (Pts) with recurrent epithelial OC who had received ≤ 2 chemotherapy regimens and no prior treatment with a VEGF or mTOR inhibitor were eligible. A two-stage design was used with second stage accrual if >6 pts had objective responses (OR) or >10 pts of the first 25 remained progression-free (PF) at six months (mo). Pre-defined end-points for a recommendation for further clinical trial evaluation included at least 15/50 with OR or 26/50 PF at six mo. Treatment included T 25 mg IV wkly and B 10 mg/kg IV q14 days on 28 day cycles. **Results:** 58 pts were enrolled (the first 50 pts are used to determine a final recommendation). Median age=62 (range 35-82). A median of 4 (range 1-23) cycles were administered. 24 were platinum-sensitive, 34 resistant. Off-study reasons included 13 adverse events and disease progression in 38. 3 refused further therapy due to toxicity. 14 of the first 50 pts had partial response (PR) (9 platinum-resistant); 25/50 remained PF (8 PR, 15 SD, 2 non-progressing) at 6 mo. Grade (gr) 3/4 toxicities occurring >2 events include: fatigue (4), stomatitis (7), hypertension (5), neutropenia (4), thrombocytopenia (4), hypokalemia (3). One rectal and one vaginal fistula, and two colonic perforations (one gr 2 and one gr 3 during cycles 3 and 1 respectively) were observed. Episodes of gr 1/2 oral, nasal, pulmonary, vaginal and gastrointestinal hemorrhage were also observed. **Conclusions:** Although the OR and PFS did not reach pre-defined standards, the numbers of OR and 6 mo PFS suggest potential enhanced activity with a combination of mTOR inhibitor with anti-angiogenic therapy. Other combinations of these targeted agents may result in more satisfactory activity with less toxicity. N01-CM-62203 (PMH) N01-CM-62208 (Southeast Phase 2) N01 CM-62209 (CCCP) N01-CM-62204 (NYCC) N01-CM-2011-0071C (Chicago) N01-CM62205 (Mayo)

Background

Pre-clinical Information

Vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) are important in the regulation of ovarian cancer (OC).
In a transgenic mouse model, RAD001 (everolimus) has been shown to play a central role in the regulation of ovarian cancer cell growth and cell cycle progression, to delay tumor onset and progression of OC.
VEGF is important in OC cell growth and in stimulation of ascites production; increased production of VEGF leads to rapid ascites accumulation, inhibition of VEGF expression decreases ascites production and cell growth.
Bevacizumab and rapamycin in combination in a mouse model of intraperitoneal cancer inhibit tumor growth more than either agent alone.

Clinical Activity

Bevacizumab Trials			
	CR/PR	PFS	OS
Cannistra (44 pts/DDP Resistant)	7 (15.9%)	4.4 mo	10.7 mo
GOG (recurrent OC)	13 (21%)	4.7 mo	17 mo
Cancer Consortium/Princess Margaret/ Phase II (Bev/CTX po)	17% (24%)	7.2 mo	
Phase II Cancer Consortium/Princess Margaret (Bev/Erlotinib)	2 (15%) 7 (SD)		

Based on these pre-clinical and clinical data suggesting additive or synergistic activity of these agents the combination of bevacizumab and temsirolimus in recurrent OC was evaluated in this study.

Entry Criteria

Disease Characteristics:

- Recurrent or persistent measurable ovarian epithelial cancer/primary peritoneal/Fallopian tube, of serous, endometrioid, mixed, or poorly differentiated histology
- Tissue (from the primary tumor or metastases) available for tumor studies
- No untreated CNS metastases.

Prior/Concurrent Therapy:

- No prior VEGF or VEGFR-targeting agents
- >4 weeks since prior major surgical procedure, open or core biopsy, or prior radiotherapy
- Prior systemic therapy of all types allowed
- </= 2 prior cytotoxic chemotherapy regimens
- No concurrent angiotensin-converting enzyme (ACE) inhibitors.
- Concurrent full-dose anticoagulants allowed
- ECOG performance status 0-1
- ANC ≥ 1,500/mm^3 ,Platelet count ≥ 75,000/mm^3, Hemoglobin ≥ 9.0 g/dL
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN), Alkaline phosphatase and AST ≤ 2.5 times ULN (≤ 5 times ULN in the presence of liver metastases Creatinine ≤ 1.5 times ULN
- Urine protein < 1+ by urinalysis or dipstick OR urine protein < 1,000 mg by 24-hour urine collection
- Fasting serum cholesterol ≤ 350 mg/dL, Triglycerides ≤ 1.5 times ULN (lipid-lowering agents allowed)
- Willing to donate blood for biomarker studies
- No intra-abdominal complications, uncontrolled hypertension, second malignancies, active infections, bleeding diathesis, parenteral nutrition

Statistical Design

- This report is a Phase II study of patients with recurrent ovarian cancer.
- Primary end-points are:
  - Tumor response
  - 6-month progression-free survival
- A modified two-stage Simon design with fixed sample size of 50 (first stage sample size of 25 and total sample size of 50) is adopted to test the null hypothesis that the true tumor response rate is at most 20% AND the true 6-month progression-free survival rate is at most 40%.
- If more than 6 of the first 25 evaluable patients enrolled achieve a response OR more than 10 are progression-free at 6 months then enrollment continued to the second stage. If not, patient accrual would be terminated and the regimen considered inactive.
  - 14 were Progression-free at 6 months
  - This study proceeded to second stage accrual
- If at least 15 of the first 50 evaluable patients enrolled achieve a response OR at least 26 of the first 50 evaluable patients are progression-free at 6 months this treatment would be recommended for further testing in this population.

Treatment Schema

Agent	Dose	Route	Days	Frequency
Temsirolimus	25 mg	IV*	1,8,15,22	q 28 days (± 3 days)
Bevacizumab	10 mg/kg	IV**	1,15	q 28 days (± 3 days)

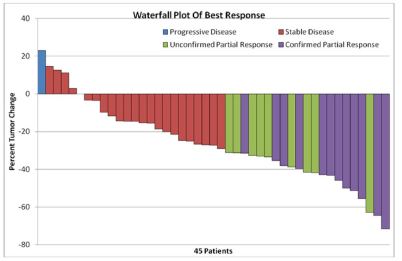
Patient Demographics (N=58)

Age	
Median (Range)	62.5 (35.0-82.0)
Performance Score	
0	29 (50.0%)
1	29 (50.0%)
Race	
Caucasian	49 (84.5%)
African American	2 (3.4%)
Asian	5 (8.6%)
Unavailable	2 (3.4%)
Ethnicity	
Hispanic	2 (3.4%)
Not Hispanic	54 (93.1%)
Not available	2 (3.4%)
Registering Institution	
Princess Margaret	34 (58.6%)
Moffitt	6 (10.3%)
Montefiore	3 (5.2%)
Mayo Clinic	
Rochester	5 (8.6%)
Florida	2 (3.4%)
Arizona	1 (1.7%)
U Chicago	2 (3.4%)
UC-Davis	5 (8.6%)
Ovarian Cancer	
Platinum-Sensitive	24 (41.4%)
Platinum-Resistant	34 (58.6%)
# of Cycles	
Median (Range)	4.0 (1.0-23.0)
Reason for Off-Study	
Refused Further Treatment	3 (5.3%)
Adverse Event	13(22.8%)
Disease Progression	38 (66.7%)
Died on Study	1 (1.8%)
Treatment Delay	2 (3.6%)

Response Data (N=53)

PR=Platinum-Resistant

Best Response	Progression-free at 6 Months: Yes	No	Total
Not Assessable	2 4%	6 11%	8 15% PR=3
Progressive Disease	0 0%	10 19%	10 19% PR=4
Partial Response	9 17%	6 11%	15 (14 of first 50 enrolled) 28% PR=9
Stable Disease	15 28%	5 9%	20 38% PR=12
Total	26 (25 of first 50 enrolled) 49%	27 51%	53 100%



•Excludes one major violation and two patients deemed clear cell and therefore Ineligible.
•10 patients had no post baseline measurement data.

Significant or Grade 3/4 Toxicity Occurring in > 1 Patient

			Grade 1 & 2 N	Grade 1 & 2 %	Grade 3 N	Grade 3 %	Grade 4 N	Grade 4 %
Body System	Toxicity	Arm						
Hemorrhage	Hemorrhage (all)	A	35	60.2	2	3.4		
Infection/Febrile Neutropenia	Infection (all)	A	8	15.4	8	13.6		
Neuropathy	Peripheral motor/sensory neuropathy	A	6	10.3				
Pain	Abdominal pain	A	11	19.0	6	10.2		
	Anal pain	A	2	3.2	1	1.7		
	Headache	A	21	36.2	2	3.4		
	Oral pain	A	5	8.6				
	Rectal pain	A	3	5.2	2	3.4		
	Dyspnea	A	8	13.8	2	3.4		
	Pneumonitis	A	1	1.7	4	6.8		
Renal /Genitourinary	Creatinine increased	A	10	17.2	1	3.4		
	Protein urine positive	A	27	46.6	2	3.4	1	1.7
	Vaginal fistula	A	2	3.4	2	3.4		
Cardiovascular	Hypertension	A	25	43.1	9	15.5		
	Myocardial ischemia	A	1	1.7	2	3.4		
	Thrombosis	A	1	1.7	2	3.4	1	1.7
Constitutional Symptoms	Fatigue	A	36	62.1	4	6.8		
	Weight loss	A	8	15.5				
	Hand-and-foot syndrome/reaction	A	4	6.8	1	1.7		
	Pruritus	A	12	20.7	2	3.4		
	Rash acneiform	A	20	34.5				
	Rash desquamating	A	15	25.9			1	1.7
Gastrointestinal	Abdominal distension	A	4	6.8				
	Anal fistula	A			1	1.7		
	Anal ulcer	A			1	1.7		
	Anorexia	A	23	39.7	1	1.7		
	Colonic obstruction	A			1	1.7		
	Colonic perforation	A	2	3.4			1	1.7
	Constipation	A	10	17.2				
	Dehydration	A	2	3.4	3	5.2		
	Diarrhea	A	15	25.9	3	5.2		
	Mucositis oral	A	24	41.4	3	5.2		
	Nausea	A	23	39.7	4	6.8		
	Rectal fistula	A			1	1.7		
	Small intestinal obstruction	A			3	5.2		
	Small intestinal perforation	A					1	1.7
	Taste alteration	A	12	20.7				
	Vomiting	A	8	13.8	4	6.8		
	Mucositis oral (clin exam)	A	15	25.9	4	6.8		
Hematology	Anemia	A	3	5.2				
	Lymphopenia	A	5	8.6	1	1.7		
	Neutropenia	A	20	34.5	4	6.8	1	1.7
	Thrombocytopenia	A	22	37.9	3	5.2	3	5.2
Metabolic/Laboratory	Hyperglycemia	A	11	19.0	1	1.7		
	Hypercholesterolemia	A	34	58.6	1	1.7		
	Hypokalemia	A	5	8.6	6	10.3		
	Hypertriglyceridemia	A	24	41.4	1	1.7		
	Hyponatremia	A	2	3.4	3	5.2	1	1.7

Summary and Conclusions

- A total of 58 patients were accrued
- The statistical analysis is based on the first 50 eligible patients accrued
- 14 patients with objective responses, and 25 patients progression-free at six months were observed.
- At the time of this analysis, the pre-determined end-points (either 15 objective responses or >25 patients progression-free at six months) of the statistical model were not met in this study. A later analysis suggests that one additional patient is observed to be progression-free at six months.
- Partial responses observed in Platinum-resistant patients suggest that this combination may be active in this chemotherapy-unresponsive population
- Although at the time of this analysis the OR and PFS did not reach pre-defined standards, the observed clinical benefit suggests potential enhanced activity with this combination of mTOR inhibitor with anti-angiogenic therapy. Other combinations of targeted agents may result in satisfactory activity with less toxicity.
- Biomarkers predictive of efficacy and/or reduced toxicity are necessary. Further phase II studies should focus on pre-selected patients having specific targets in order to achieve improved benefits of combination targeted therapy
- All 58 patients are evaluable for adverse events. Thirty-seven patients experienced grade 3+ adverse events at least possibly related to treatment suggesting that this combination exhibits excessive toxicity in ovarian cancer patients.