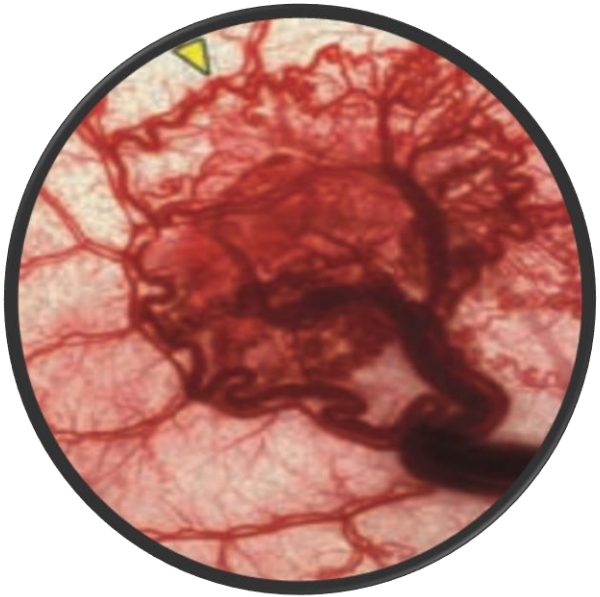
ASCO 2016: GOG-0213 Updates



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Disclosures

- Gynecologic Oncology Group
  - Genentech provided bevacizumab and support to the NCI/CTEP for this study
- Robert L. Coleman, MD
  - Roche/Genentech – research funding/travel for other studies

Angiogenesis as a Target: Ovarian

Study	Agent	Target	HR-PFS (95% CI)	HR-OS (95% CI)
GOG 218[1]	Bevacizumab	VEGF Ligand	**0.72 (0.63-0.82)**	0.89 (0.75-1.04)
ICON7[2]	Bevacizumab		**0.81 (0.70-0.94)**	0.99 (0.85-1.14)
AURELIA[5]	Bevacizumab		**0.48 (0.38-0.60)**	0.85 (0.66-1.08)
OCEANS[7]	Bevacizumab		**0.53 (0.41-0.70)**	0.96 (0.76-1.21)
GOG-213[9]	Bevacizuamb		**0.61 (0.52-0.72)**	**0.83 (0.68-1.005)***
AGO-OVAR12[3]	Nintedanib	VEGFR, FGFR, PDGFR	**0.84 (0.72-0.98)**	NR
AGO-OVAR16[4]	Pazopanib		**0.77 (0.64-0.91)**	0.99 (0.75-1.32)
ICON6[8]	Cediranib	VEGFR	**0.57 (0.44-0.74)**	0.76 (0.55-1.05)
TRINOVA-1[6]	Trebananib	Ang ligand	**0.66 (0.57-0.77)**	0.86 (0.69-1.08)

***Analysis based on 45 patients misclassified in the PFI stratification**

1. Burger RA et al. *N Engl J Med*. 2011;365:2473–2483.
2. Perren TJ et al . *N Engl J Med*. 2011;365:2484–2496.
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7. Aghajanian C et al. *J Clin Oncol*. 2012;30:2039–2045.
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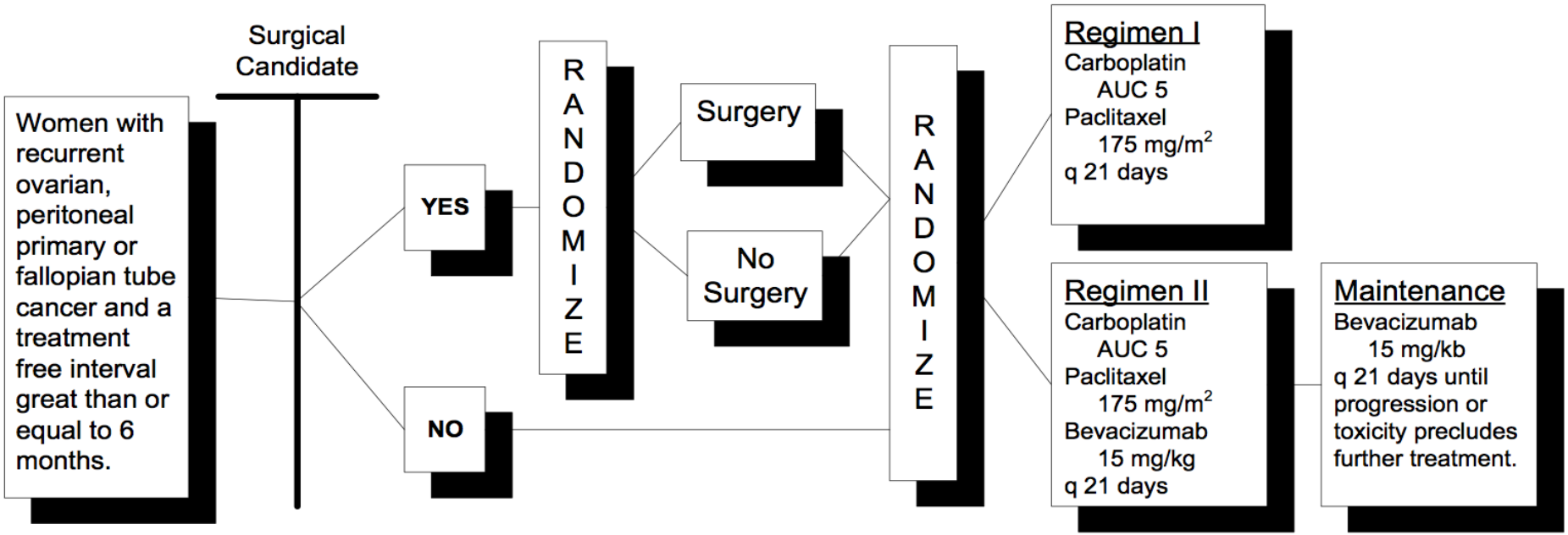
9. Coleman, RL, SGO 2015 LBA3

GOG 213: Schema



GOG 213: Primary Objectives

- **Objective #1:** To determine if the addition of bevacizumab to paclitaxel and carboplatin followed by maintenance bevacizumab will **increase overall survival** relative to paclitaxel and carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer
- **Objective #2:** To determine the effect of secondary cytoreduction followed by chemotherapy on **overall survival** in patients with platinum-sensitive recurrent ovarian cancer

GOG 213: Secondary Objectives

- **Objective #1:** To determine the effect of bevacizumab/paclitaxel/carboplatin vs. paclitaxel/carboplatin on PFS
- **Objective #2:** To determine rate of allergy and adverse events
- **Objective #3:** To assess the effect of bevacizumab combination vs paclitaxel/carboplatin on QoL
- **Objective #4 (pending):** To assess the effect of surgery followed by bevacizumab combination vs chemotherapy alone on QoL

GOG 213: Eligibility

- Recurrent epithelial, peritoneal or fallopian tube cancer
- Recurrence:
  - "Clinically Evident" (measurable or assessable)
  - Mass or symptomatic ascites with elevated CA125 (2X) or Bx
  - CA125 ≥ 2X ULN, CA125 > 100 or CA125 < 100 and confirmed
- CR front-line therapy + PFS ≥ 6 mos
  - Clinical CR: negative PE, CA125
  - Pathological CR: Reassessment procedure SLL
  - Front-line: includes maintenance (recurrence must be ≥ 6 mos after maintenance)
  - Prior bevacizumab allowed

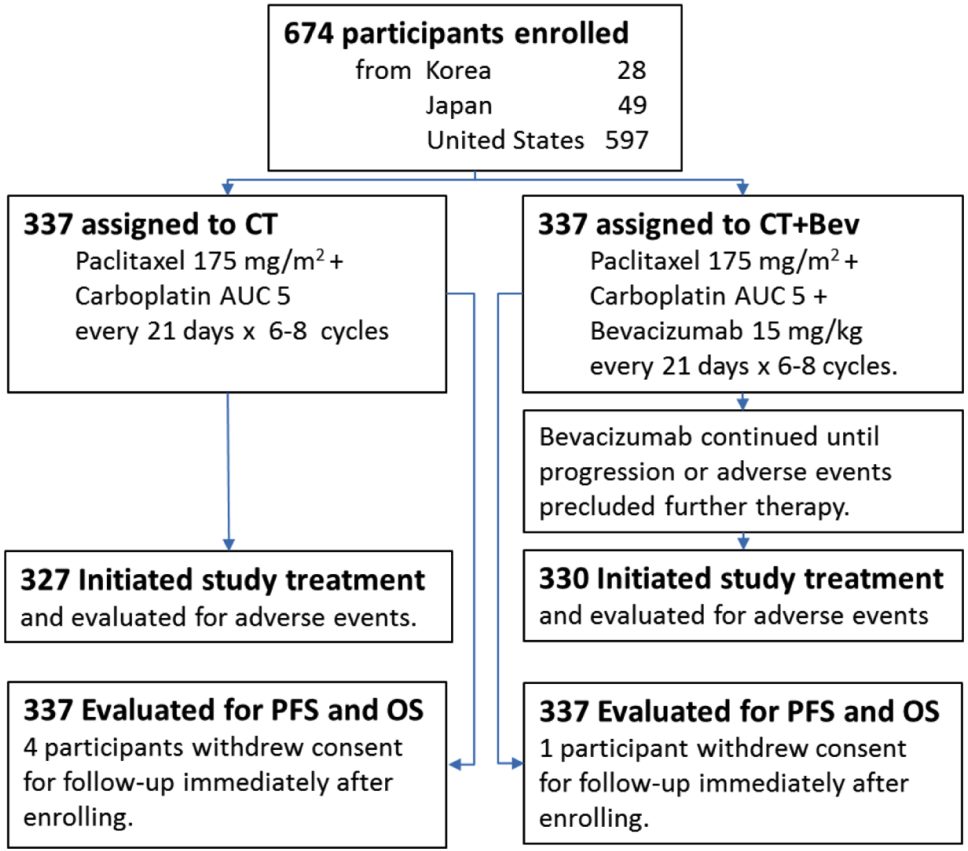
GOG 213: Ineligibility

- Concurrent therapy
- More than one prior regimen (excluding maintenance)
- Need for TPN
- Symptoms or diagnosis of bowel obstruction
- Grade 2+ neuropathy
- Hypersensitivity not controlled with desensitization
- Major surgery within 4 weeks

Statistical Design

- Primary endpoint for both primary objectives is **OS**
- Assumption of no interaction between the two randomizations
- Alpha set **two-sided at 0.05** in each randomized comparison
- Estimated median OS of control arm: **22 months**
- Stratification variables:
  - **Participation in Objective 2 (surgical randomization)**
  - **Platinum-Free Interval (6-12, ≥12 months)**
- Treatment effect based on prior bevacizumab was a preplanned analysis
- Targeted adjusted HR: 0.75 (sample: 660 patients)
- Analysis considered mature: 214 events in control arm (11/5/14)

CONSORT Diagram (Chemotherapy Analysis)



Demographics (N=674)

Characteristic	PC (n=337)	PC + B (n=337)	Total (n=674)
Prior Bevacizumab			
Yes	33 (10%)	34 (10%)	67 (10%)
No	303 (90%)	303 (90%)	606 (90%)
Unspecified	1 (0.3%)	0	1 (0.1%)
Cytoreductive Surgery			
Randomized, No Surgery Randomized, Surgery	27 (8%) 27 (8%)	27 (8%) 26 (8%)	54 (8%) 53 (8%)
Not Randomized	283 (84%)	284 (84%)	567 (84%)
Prior Platinum-Free Interval*			
6-12 months	105 (31%)	105 (31%)	210 (31%)
>12 months	232 (69%)	232 (69%)	464 (69%)
Measurable disease			
No	50 (15%)	63(19%)	113 (17%)
Yes	287 (85%)	274 (81%)	561 (83%)

* Declared on enrollment onto the study

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GOG 213: Adverse Events of Special Interest

Patients, %	PC (n=327)	PC + B (n=330)	P
Thromboembolism, grades ≥ 3	4 (1%)	13 (4%)	0.05
Arterial Thromboembolism, grade ≥3	2 (<1%)	8 (2%)	NS
Non-CNS bleeding, grades ≥3	3 (1%)	6 (2%)	NS
Infection, grades ≥ 3	19 (6%)	43 (13%)	0.002
Neutropenia, grade ≥3	255 (78%)	276 (84%)	NS
Febrile neutropenia, grade ≥3	9 (3%)	20 (6%)	NS
Hypertension, grade ≥3	2 (<1%)	39 (12%)	<0.001
GI perforation, fistula/abscess, grade ≥ 3	3 (1%)	6 (2%)	NS
Proteinuria, grade ≥3	0	27 (8%)	<0.001
Reversible posterior leukoencephalopathy, all grades	0	2 (<1%)	NS
Neuropathy, grades ≥ 2	61 (19%)	66 (20%)	NS
Joint pain, grades ≥ 3	15 (5%)	50 (15%)	<0.001
Wound-healing complication, grades ≥3	0	3 (1%)	NS

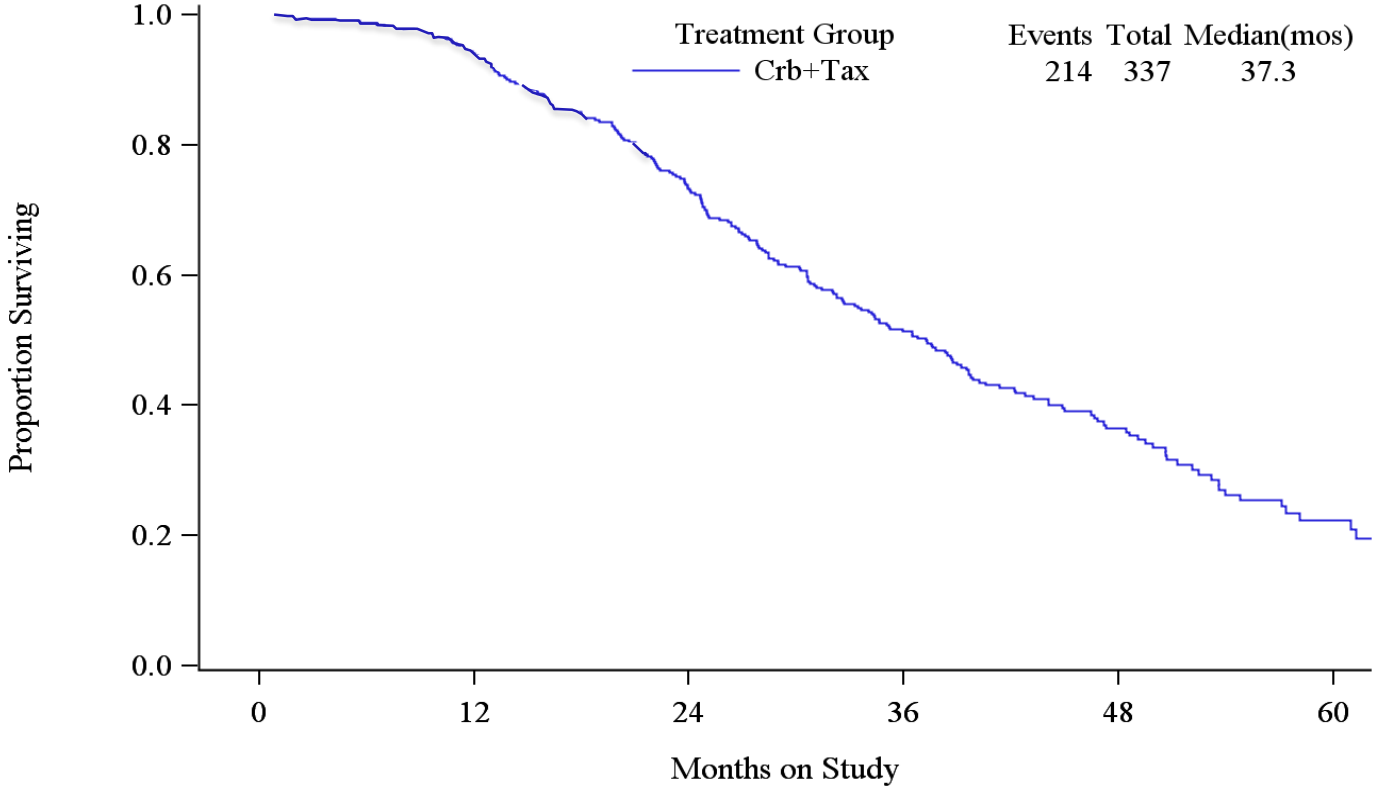
GOG 213: Adverse Events of Special Interest

Patients, %	PC (n=327)	PC + B (n=330)	P
Thromboembolism, grades ≥ 3	4 (1%)	13 (4%)	0.05
Arterial Thromboembolism, grade ≥3	2 (<1%)	8 (2%)	NS
Non-CNS bleeding, grades ≥3	3 (1%)	6 (2%)	NS
Infection, grades ≥ 3	19 (6%)	43 (13%)	0.002
Neutropenia, grade ≥3	255 (78%)	276 (84%)	NS
Febrile neutropenia, grade ≥3	9 (3%)	20 (6%)	NS
Hypertension, grade ≥3	2 (<1%)	39 (12%)	<0.001
GI perforation, fistula/abscess, grade ≥ 3	3 (1%)	6 (2%)	NS
Proteinuria, grade ≥3	0	27 (8%)	<0.001
Reversible posterior leukoencephalopathy, all grades	0	2 (<1%)	NS
Neuropathy, grades ≥ 3	61 (19%)	66 (20%)	NS
Joint pain, grades ≥ 3	15 (5%)	50 (15%)	<0.001
Wound-healing complication, grades ≥3	0	3 (1%)	NS

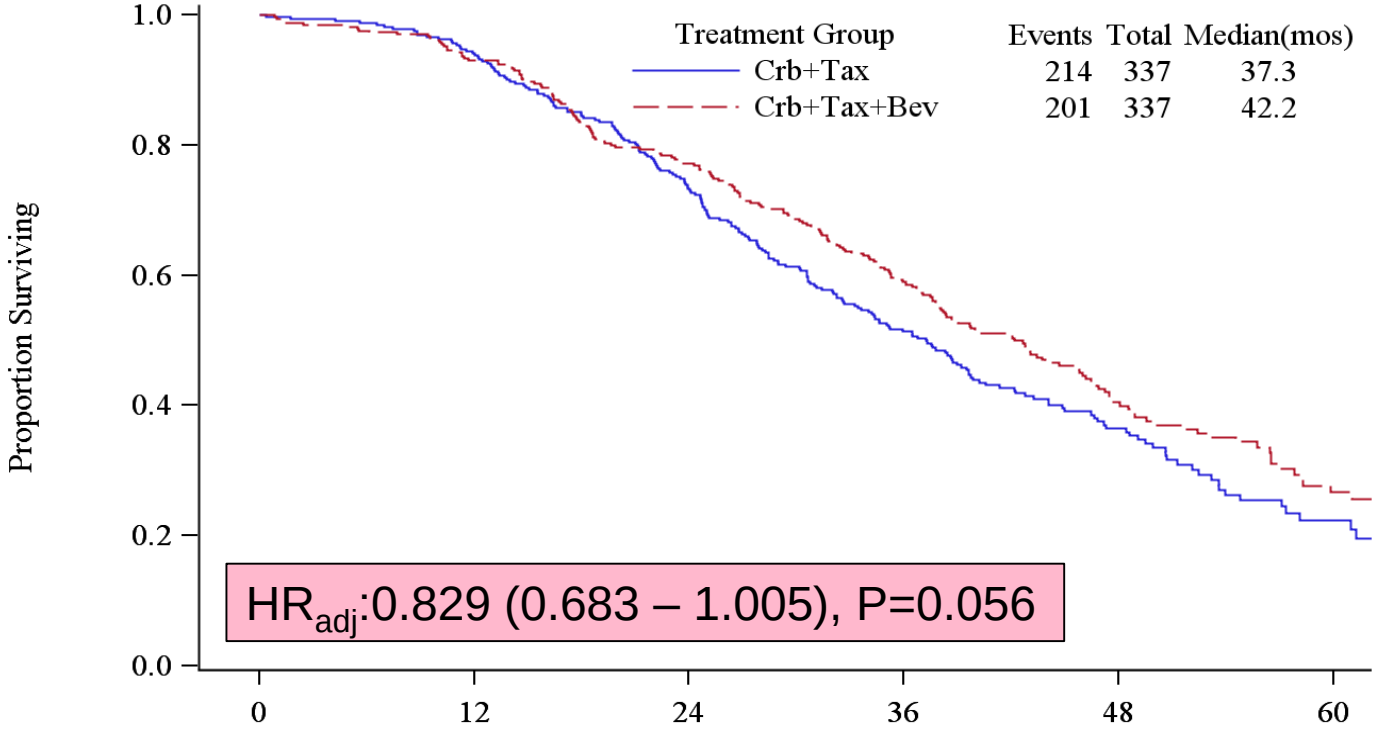
GOG 213: Adverse Events of Special Interest

Patients, %	PC (n=327)	PC + B (n=330)	P
Allergy – hypersensitivity	82 (25%)	88 (27%)	NS
Death			
Treatment-Related	2 (<1%)	9 (2.4%)	NS
Infection – Sepsis, non-GI	0 (<1%)	2 (<1%)	NS
Myelodysplasia	1 (<1%)	1 (<1%)	NS
Secondary Malignancy	1 (<1%)	1 (<1%)	NS
Unspecified	0	5 (1.5%)	NS

GOG 213 Treatment Outcome: OS



GOG 213 Treatment Outcome: OS*

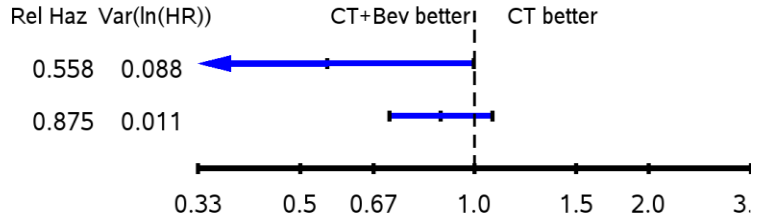


Crb+Tax	337	303	234	152	69	18
Crb+Tax+Bev	337	306	253	183	75	28

*** Includes 45 patients (6.7%) errantly misclassified on PFI strata**

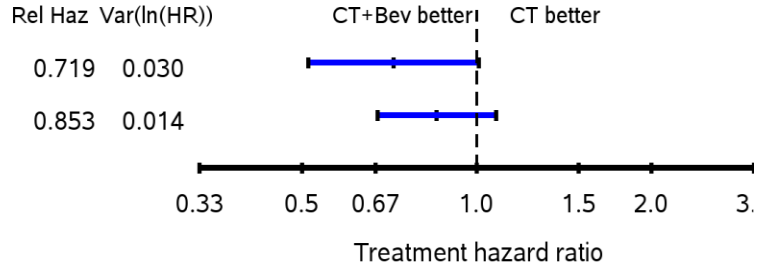
Stratification Variables: OS

Objective 2



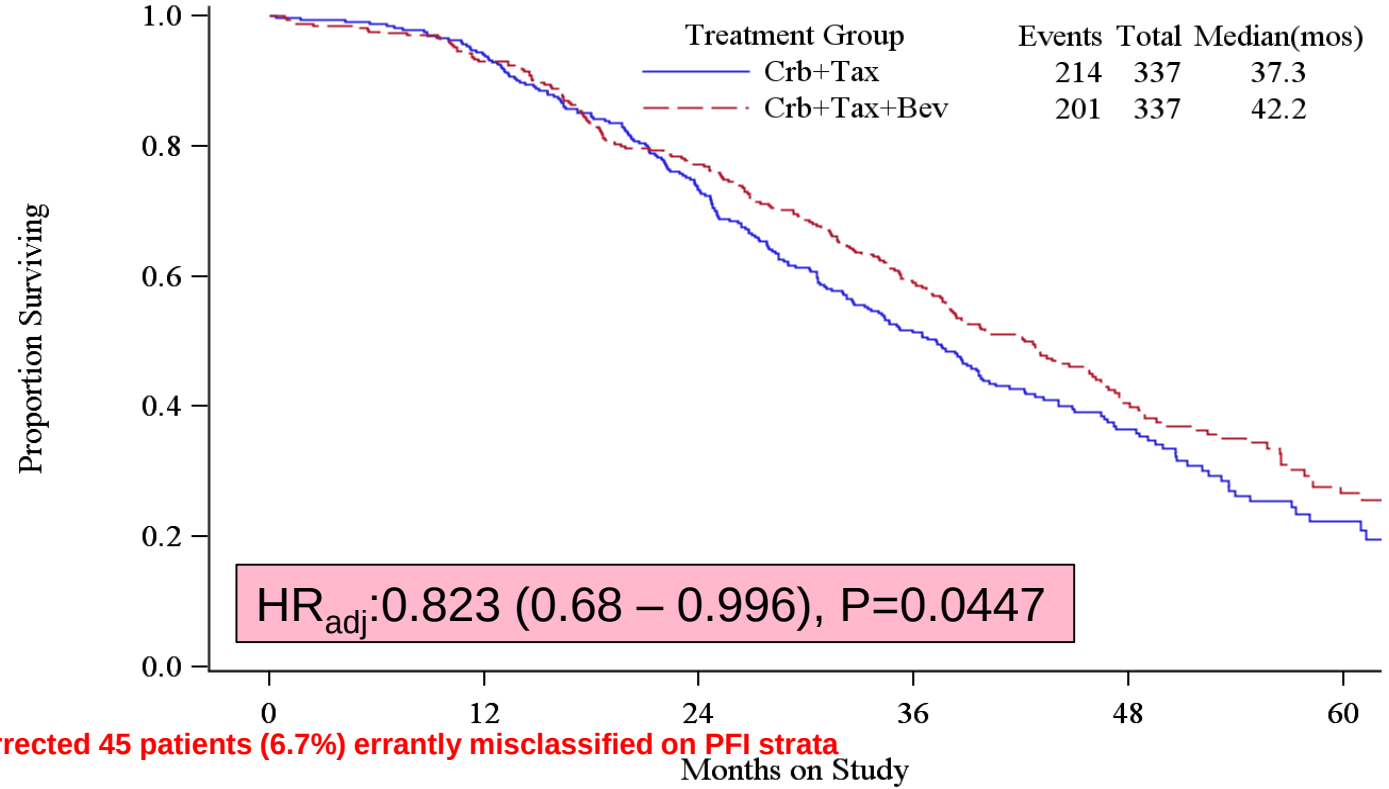
N=107 (16%)
N=567 (84%)

PFI



N=181 (27%)
N=493 (73%)

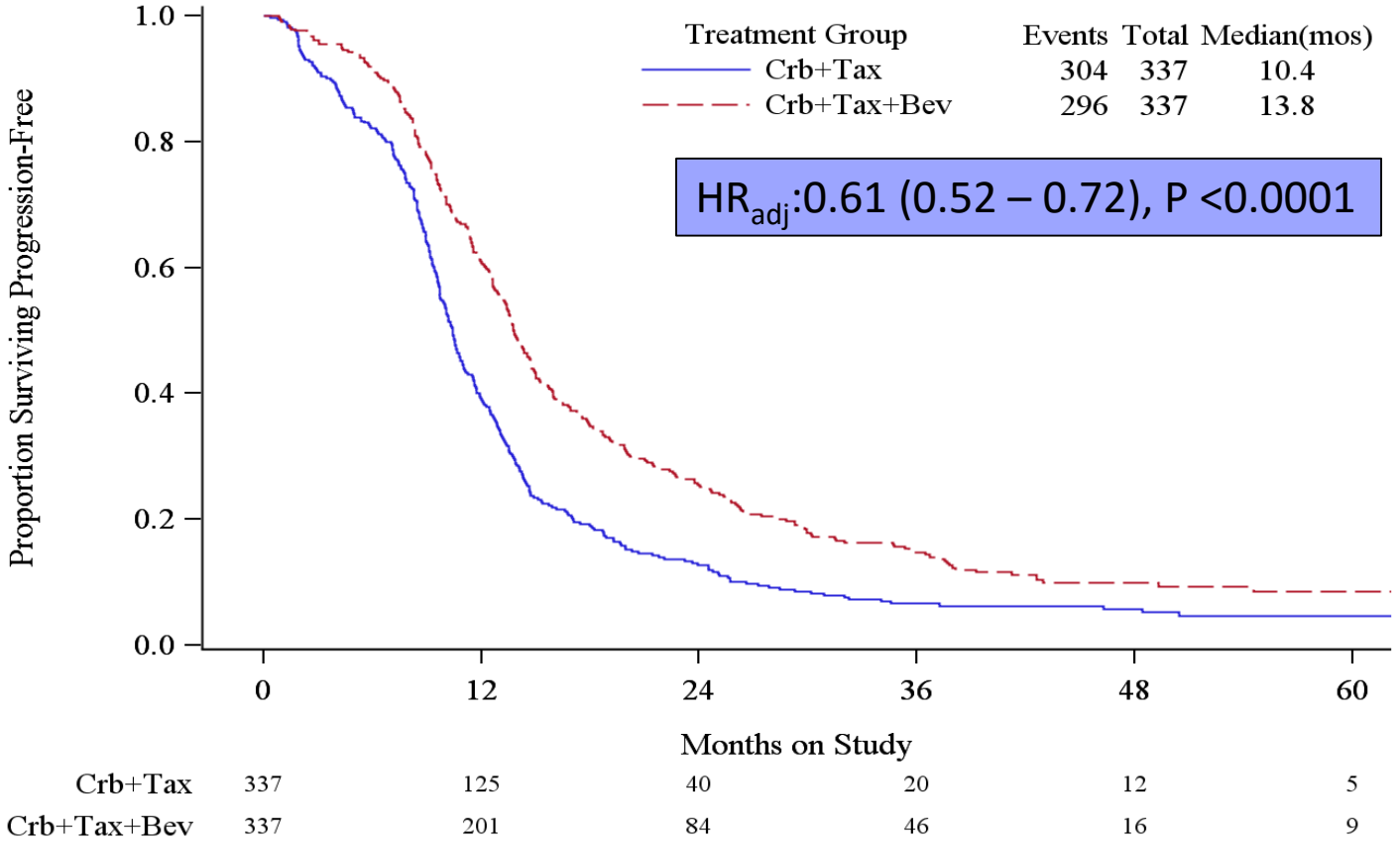
GOG 213 Treatment Outcome: OS*



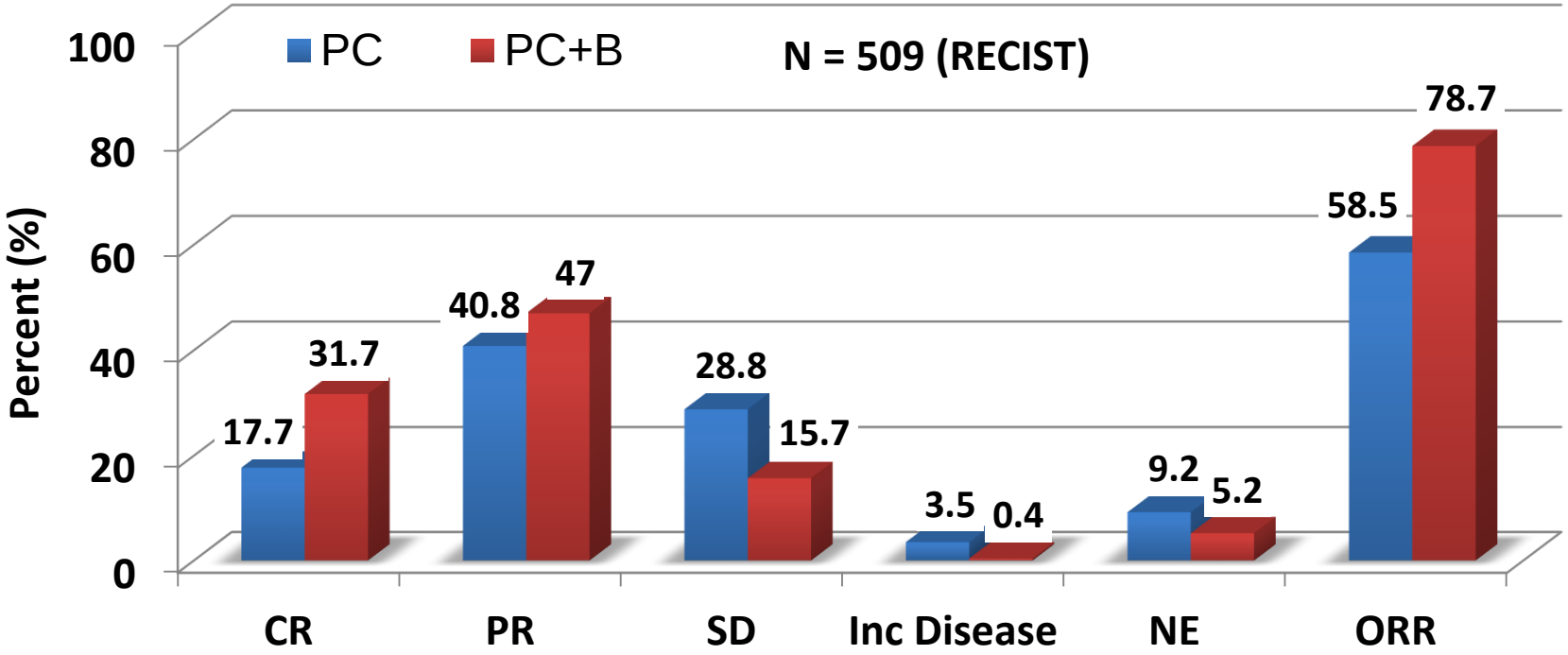
HR_{adj}:0.823 (0.68 – 0.996), P=0.0447

*** Includes corrected 45 patients (6.7%) errantly misclassified on PFI strata**

GOG 213 Treatment Outcome: PFS

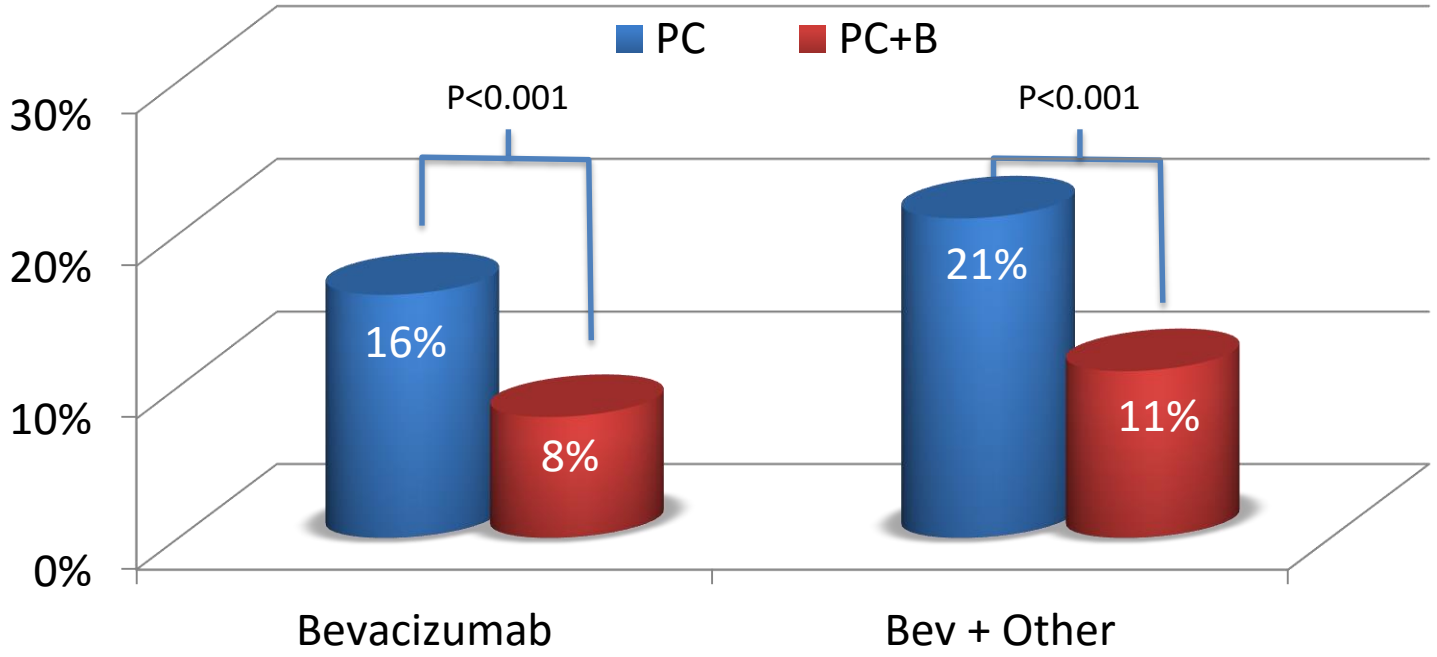


GOG 213 Treatment Outcomes: Response



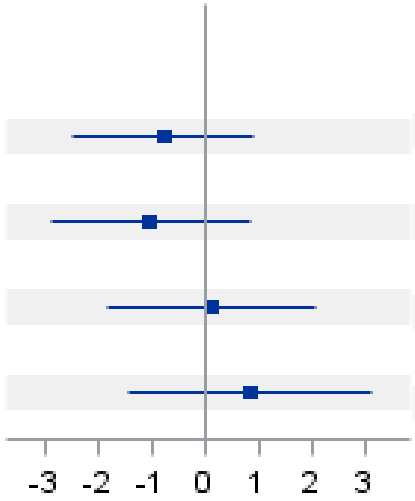
P < 0.0001

Anti-Angiogenesis Use in the Immediate Next Line of Therapy



QoL: FACT-O TOI Score

Assessment Time	Means(SE)		Difference(95% CI)	P-Value
	No Bev	Bev		
Pre-cycle 1	75.8 (0.8)	75.3 (0.9)		
Pre-cycle 3	74.2 (1.0)	73.4 (0.9)		0.351
Pre-cycle 6	73.3 (1.0)	72.3 (1.0)		0.276
6 Months post cycle 1	77.1 (1.0)	77.2 (1.0)		0.897
12 Months post cycle 1	77.0 (1.1)	77.8 (1.0)		0.479



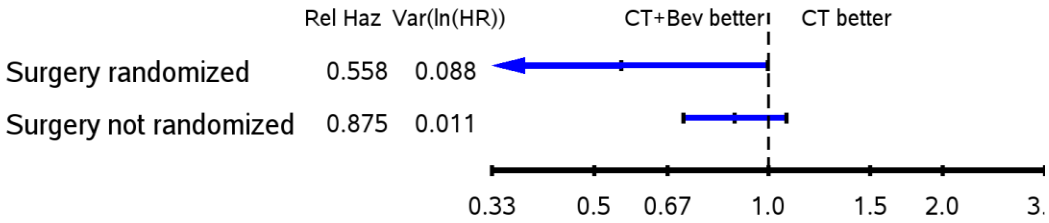
Means at baseline are raw means. Means at follow-ups are least squared means estimated from the fitted linear mixed model.

Conclusions: Primary Analysis

- Paclitaxel + carboplatin and bevacizumab extended OS in patients with platinum-sensitive recurrent ovarian cancer
  - Significant underestimation of OS in this population
  - Sensitivity analysis suggest results are robust
- The combination was associated with a significant improvement in PFS
- More toxicity was observed with concomitant bevacizumab and bevacizumab maintenance, no new safety signals were observed
- No significant difference in patient-reported quality of life as measured by the FACT-O TOI
- Surgical endpoints are pending

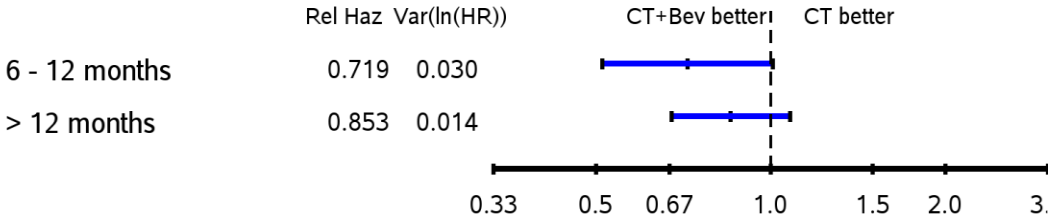
Forest Plot: OS

Objective 2



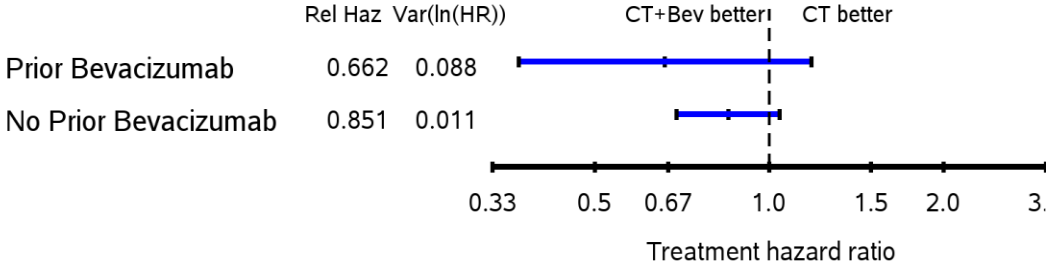
N=107 (16%)
N=567 (84%)

PFI



N=181 (27%)
N=493 (73%)

Prior Bev



N=67 (10%)
N=606 (90%)

Abstract: 5523
Poster Board: 346

Randomized phase III trial of carboplatin/paclitaxel alone (CP) or in combination with bevacizumab followed by bevacizumab (CPB) and secondary cytoreduction surgery in platinum-sensitive recurrent ovarian cancer– GOG0213, an NRG Oncology/GOG Study: Analysis of the prior bevacizumab exposure population

Robert L. Coleman[1], Mark F. Brady[2], Thomas J Herzog[3], Deborah Kay Armstrong[4], Paul Sabbatini[5], Joan L. Walker[6], Byoung Gie Kim[7], Keiichi Fujiwara[8], Krishnansu S. Tewari[9], David M. O'Malley[10]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]NRG Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; [3]The University of Cincinnati Cancer Institute, Cincinnati, OH; [4]Johns Hopkins Kimmel Cancer Ctr, Baltimore, MD; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Stephenson Cancer Center, OUHSC, Oklahoma City, OK; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [8]Saitama Medical University International Medical Ctr, Hidaka-Shi, Japan; [9]Univ of California Irvine Medical Ctr, Orange, CA; [10]The Ohio State University College of Medicine, Columbus, OH

BACKGROUND

- GOG 213 is a bifactorial, phase III, randomized trial designed to study the efficacy and tolerability of the incorporation of bevacizumab (B) and secondary cytoreduction in women with platinum sensitive recurrent EOC. The primary endpoint was OS.
- The database was locked on 11/4/14 when the protocol-specified 214 deaths had occurred in the control arm, at which point 674 patients were evaluable to assess the impact of anti-VEGF therapy.
- We recently reported that patients receiving C (AUC5) and P (175 mg/m2) with B (15 mg/kg) q21 days followed by B maintenance (15 mg/kg) had a reduction in the hazard for death of 17.1% (HR: 0.829, 95% CI: 0.683-1.005), the hazard for progression of 38.6% (HR: 0.614, 95% CI: 0.522-0.722) and a higher overall (79% vs. 59%, P<0.0001) and complete (32% vs. 18%, P<0.001) response rate compared with patients treated with chemotherapy alone (1).
- We also demonstrated that while toxicity was greater in the B containing arm, health-related QoL, as measured by the FACT-O TOI, was not significantly different between the arms. However, while receiving CPB, patients may experience lower physical functioning with recovery to baseline during maintenance B.(2)
- The biological processes governing angiogenesis in the tumor microenvironment are both complex and poorly understood. While retention of phenotypic leveraging of alterative angiogenic growth pathways could result in poor tumor response on retreatment with B, loss of this phenotype might have no lasting impact. Thus, the clinical implication of prior B treatment on subsequent B use is unknown. Ongoing clinical trials are evaluating whether prior bevacizumab might impact outcomes with subsequent B treatment.(3)

OBJECTIVE

- **To characterize the clinical efficacy and safety of bevacizumab re-treatment in patients with recurrent, platinum-sensitive ovarian cancer enrolled in GOG0213 who were previously treated with bevacizumab.**

STUDY DESIGN

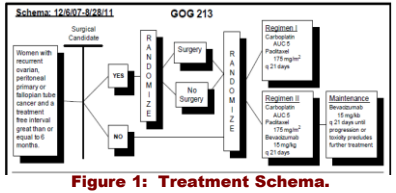


Figure 1: Treatment Schema.

ELIGIBILITY

- Histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent (eligible cell types: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, adenocarcinoma not otherwise specified [NOS]).
- Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles) and a treatment-free interval without clinical evidence of progressive disease of 6+ months from completion of front-line chemotherapy. Front-line therapy may have included a biologic agent (i.e. bevacizumab).
- Front-line treatment may include maintenance therapy following complete clinical or pathological response. However, maintenance cytotoxic chemotherapy must be discontinued for a minimum of 6 months prior to documentation of recurrent disease. Patients receiving maintenance biological therapy or hormonal therapy are ELIGIBLE provided their recurrence is documented more than 6 months from primary cytotoxic chemotherapy completion (includes maintenance chemotherapy) AND a minimum 4 weeks has elapsed since their last infusion of biological therapy.
- Patients must have clinically evident recurrent disease for the purpose of this study.
- GOG Performance Status of 0, 1, or 2.
- Patients must be at least 18 years old.
- Patients must have NOT received more than one previous regimen of chemotherapy (maintenance is not considered a second regimen); or concurrent immunotherapy, or radiotherapy; or prior radiotherapy to any portion of the abdominal cavity or pelvis.
- No major surgical procedure, open biopsy, dental extractions or other dental surgery/procedure that results in an open wound, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.

STRATIFICATION VARIABLES

- Treatment free interval at first recurrence (6-12, 12+ months)
- Participation in Objective 2 (Surgical Cytoreduction vs. No Surgical cytoreduction)

ANALYSIS

- **The current objective was a pre-specified and planned supplemental analysis of the primary endpoint, overall survival.**

RESULTS

Summary

- From 674 patients randomized to CP (n = 337) or CPB (n = 337), 69 (10.3%, n=34, CP, n=35 CPB) had previously received bevacizumab as part of primary and/or maintenance therapy.
- Patient Characteristics were similar to the overall treatment population
- In this subpopulation, the median OS of adding bevacizumab to chemotherapy did not differ from that of chemotherapy alone (CPB: 36.8 mos. vs. CP: 32.0 mos., HR: 0.76, 95% CI: 0.44-1.34). **Figure 2.**
- The median PFS for CPB and CP were similar (median PFS 10.7 mos. vs. 9.8 mos., HR: 0.84, 95%CI: 0.52-1.37, respectively). **Figure 3**.
- Despite the small sample size, prior bevacizumab treatment did not appear to negatively impact OS and PFS, although it does preclude more definitive conclusions on bevacizumab efficacy
- 56 patients (n=28 each arm) had RECIST measurable disease to assess objective response. Overall response was significantly higher in the CPB cohort (82% vs. 54%, P=0.044); in addition, the rate of complete response was 3 fold higher (32% vs. 11%, P<0.02).
- Bevacizumab increased the rate of grade 3-4 hypertension from 0% to 6%. All grade proteinuria, non-CNS bleeding and neutropenia were higher in the PCB arm, however, the rate of gastrointestinal perforation/abscess was not significantly increased (0% in both arms). **TABLE 1.**

Figure 2:

Prior treatment with bevacizumab had no significant impact on O the Intent to Treat (ITT population.

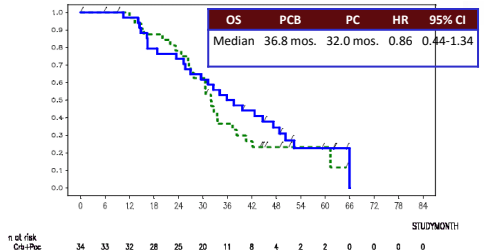


Figure 3:

Prior treatment with bevacizumab had no significant impact on P the Intent to Treat (ITT population.

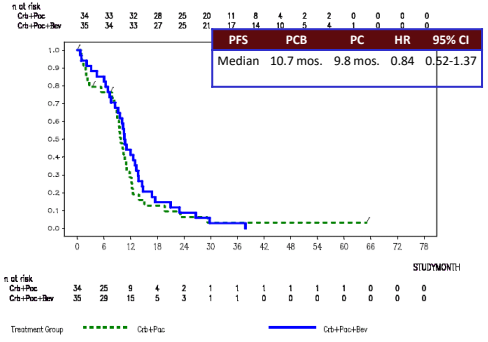


Table I. Adverse Events of Special Interest (End of Treatment + 6 mos.)

Patients, %	CP (n=35)	CP + BV (n=33)
Any All Grade AE of Special Interest	4 (11%)	21(64%)
AE of Special Interest, grade ≥3	2 (6%)	7 (21%)
Non-CNS bleeding	2 (6%)	15 (46%)
CHF	0 (0%)	1 (3%)
Fistula/Abscess, Non-gastrointestinal (GI)	0 (0%)	0 (0%)
GI perforation, fistula/abscess, all grades	0 (0%)	0 (0%)
Hypertension	0 (0%)	9 (28%)
Neutropenia	2 (6%)	4 (12%)
RPLS, all grade	0 (0%)	0 (0%)
Proteinuria	0 (0%)	5 (15%)
Thromboembolic event – arterial	1 (3%)	1 (3%)
Thromboembolic event – venous	0 (0%)	0 (0%)
Wound-healing complication	0 (0%)	2 (6%)
Deaths not due to progression	1 (3%)	0 (0%)

CONCLUSION

Re-treatment with bevacizumab in GOG0213 did not appear to negatively impact subsequent bevacizumab treatment. While the directionality of bevacizumab effect on OS and PFS are consistent with the ITT population, the limited sample size precludes more definitive conclusion. Higher rate of overall and complete response rates were observed and prior bevacizumab did not negatively impact safety.

REFERENCES

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2. Basen-Engquist K, Huang HQ, Herzog TJ, et al., J Clin Oncol 2015 33: Suppl; Abstr 5525
3. Http://clinicaltrials.gov Study NCT01802749 – MITO16/MANGO2b

Grant Support

1. NIH grants P50 CA098258, CA27469, CA37517
2. Genentech/Roche
3. Ann Rife Cox Chair in Gynecology
4. Judy Reis Ovarian Cancer Foundation

The authors would like to acknowledge the Genentech-Roche study team for their thoughtful dialogue and review

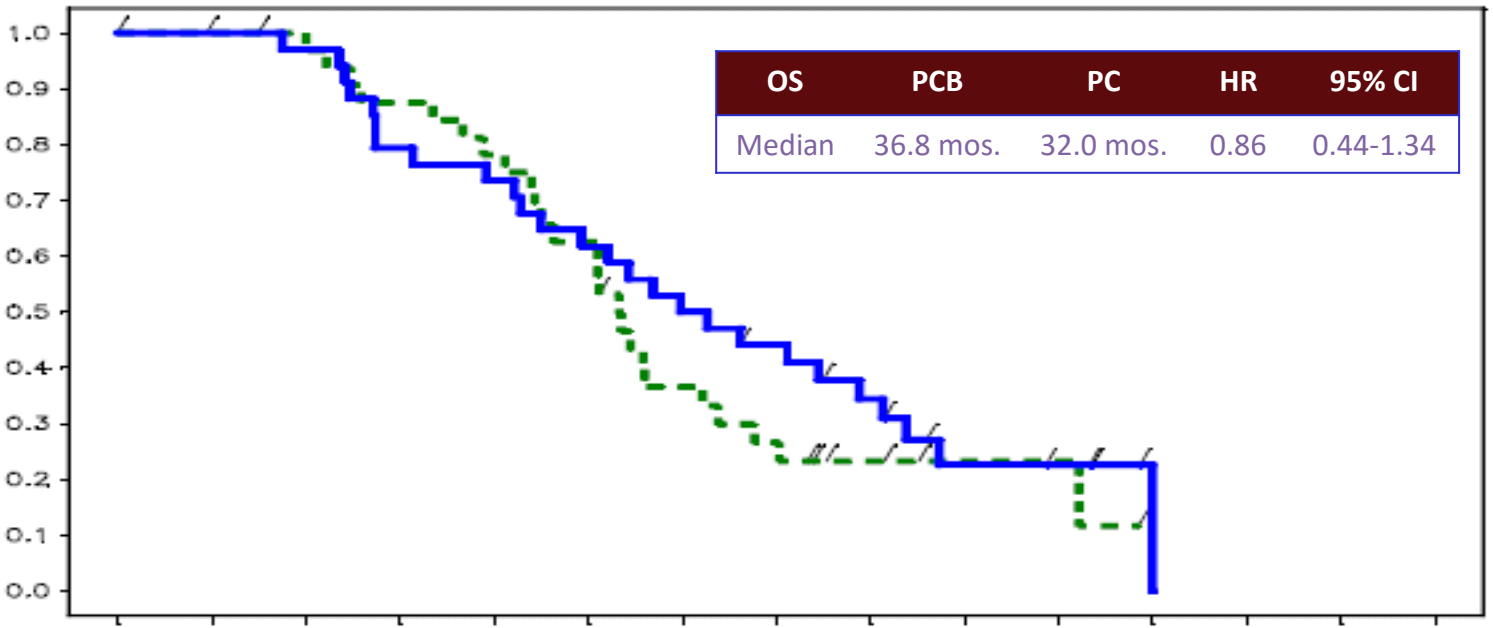
GOG-213: Bev after Bev Analysis

- 69 patients (10%, N=34 PC, N=35 PCB) received prior bevacizumab
- Demographics were similar but with slightly longer platinum-free interval in the control group
- 56 patients (N=28 each arm) had RECIST measurable disease

GOG-213 Bev after Bev: Toxicity

Patients, %	CP (n=35)	CP + BV (n=33)
Any All Grade AE of Special Interest	4 (11%)	21(64%)
AE of Special Interest, grade ≥3	2 (6%)	7 (21%)
Non-CNS bleeding	2 (6%)	15 (46%)
CHF	0 (0%)	1 (3%)
Fistula/Abscess, Non-gastrointestinal (GI)	0 (0%)	0 (0%)
GI perforation, fistula/abscess, all grades	0 (0%)	0 (0%)
Hypertension	0 (0%)	9 (28%)
Neutropenia	2 (6%)	4 (12%)
RPLS, all grade	0 (0%)	0 (0%)
Proteinuria	0 (0%)	5 (15%)
Thromboembolic event – arterial	1 (3%)	1 (3%)
Thromboembolic event – venous	0 (0%)	0 (0%)
Wound-healing complication	0 (0%)	2 (6%)
Deaths not due to progression	1 (3%)	0 (0%)

GOG-213 Bev after Bev: OS



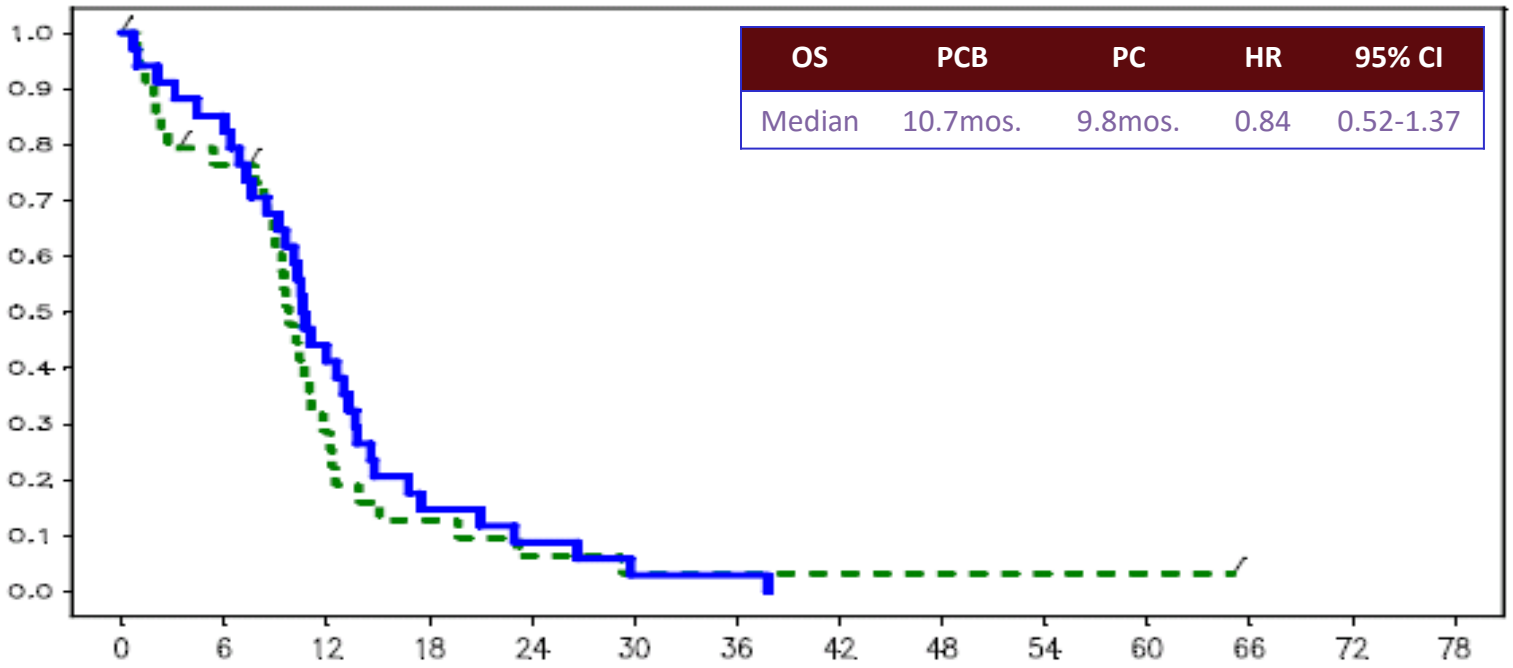
OS	PCB	PC	HR	95% CI
Median	36.8 mos.	32.0 mos.	0.86	0.44-1.34

n at risk

Crb+Poc	34	33	32	28	25	20	11	8	4	2	2	0	0	0	0
Crb+Poc+Bev	35	34	33	27	25	21	17	14	10	5	4	1	0	0	0

Randomized treatment — Crb+Poc — Crb+Poc+Bev

GOG-213: Bev after Bev PFS

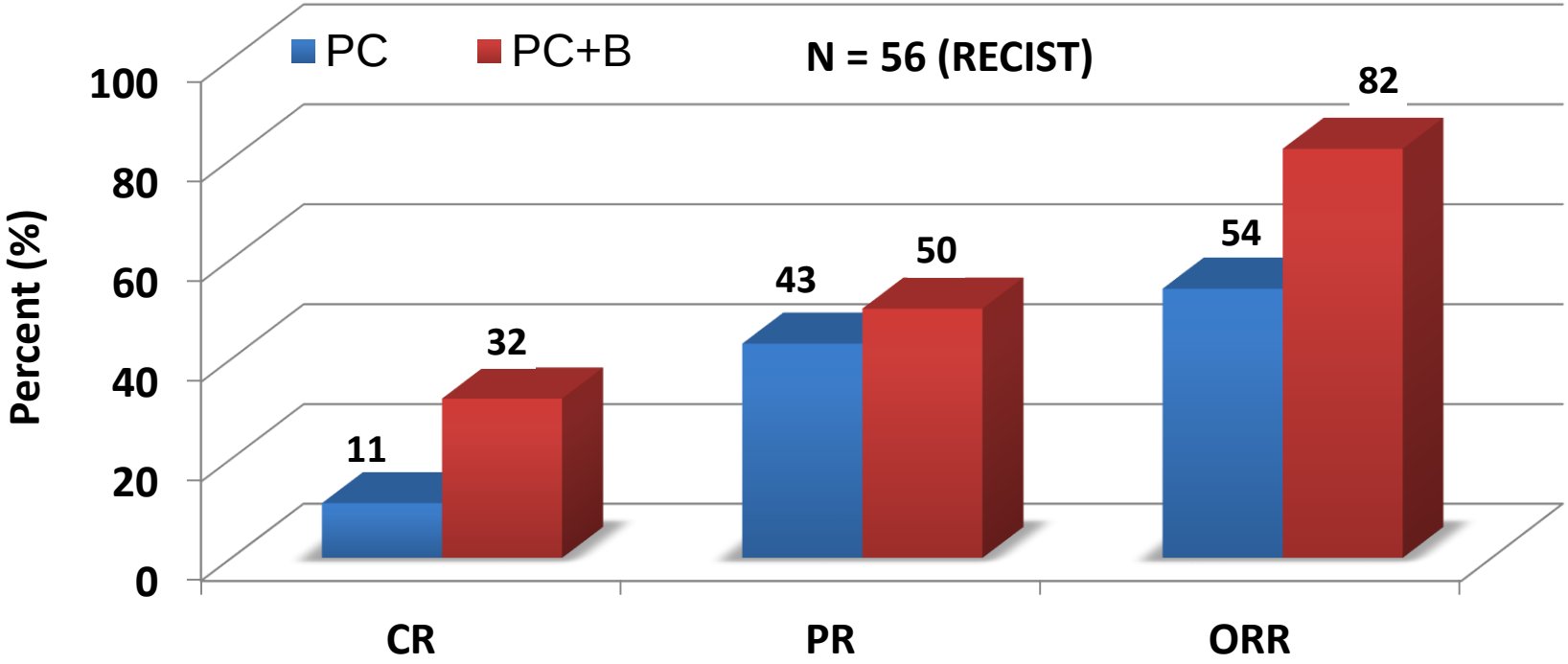


OS	PCB	PC	HR	95% CI
Median	10.7mos.	9.8mos.	0.84	0.52-1.37

n at risk													
Crb+Pac	34	25	9	4	2	1	1	1	1	1	1	0	0	0
Crb+Pac+Bev	35	29	15	5	3	1	1	0	0	0	0	0	0	0

Treatment Group — Crb+Pac — Crb+Pac+Bev

GOG 213 Bev after Bev: Response



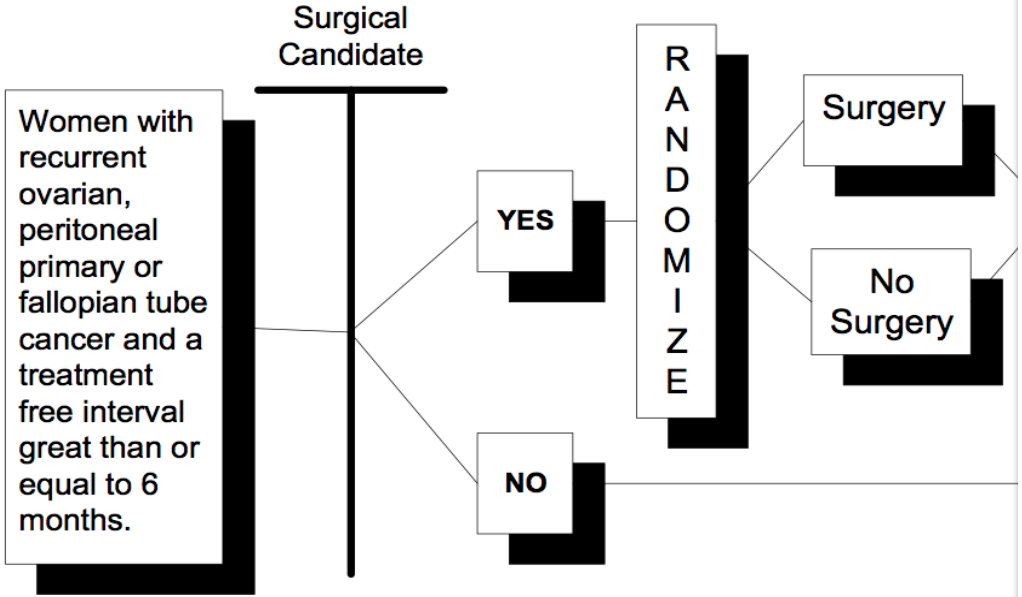
P = 0.044

Conclusions: Bev after Bev Analysis

- Limited inference due to small sample size but no definitive signal of a negative impact
- Toxicity was similar to prior bevacizumab naïve patient, but demonstrated consistent AE's of special interest in bevacizumab treated patients
- Objective response was similar to primary analysis including a near tripling of the CR rate

GOG 213: Schema (Current)

Schema: 12/6/07-8/28/11



Chemotherapy is now Physician's Choice

- **Paclitaxel/Carboplatin ± Bev**
- **Gemcitabine/Carboplatin ± Bev**

NOT ELIGIBLE

GOG-213: Special Acknowledgements

- Study Co-Chairs:
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  - USA: 45 member institutions
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  - Japanese GOG
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Thank You!