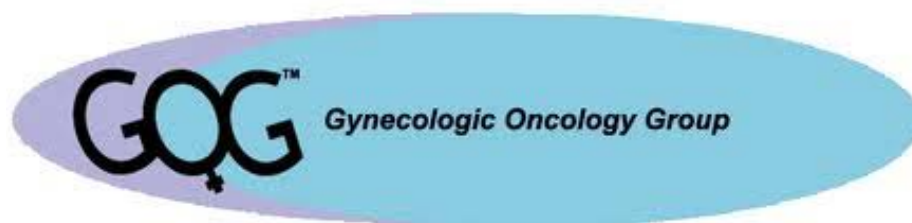


# INCORPORATION OF BEVACIZUMAB IN THE TREATMENT OF RECURRENT AND METASTATIC CERVICAL CANCER

## GOG 240: A PHASE 3 RANDOMIZED TRIAL OF THE GYNECOLOGIC ONCOLOGY GROUP

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MM Leitao, HE Michael, BJ Monk



# Disclosures

- Gynecologic Oncology Group
  - Genentech provided bevacizumab to the NCI for this study
- KS Tewari
  - Participated in Genentech/Roche conference calls to discuss the development of bevacizumab in cervical cancer
    - Consultancy fees, honoraria, travel, accommodations – not accepted
  - Advisory/Speaker's Bureau
    - Vermillion, Ovagene
  - Extramural funding (PI)
    - NIH R21, Intuitive Surgical, Queen of Hearts Foundation

# Recurrent and Metastatic Cervical Cancer

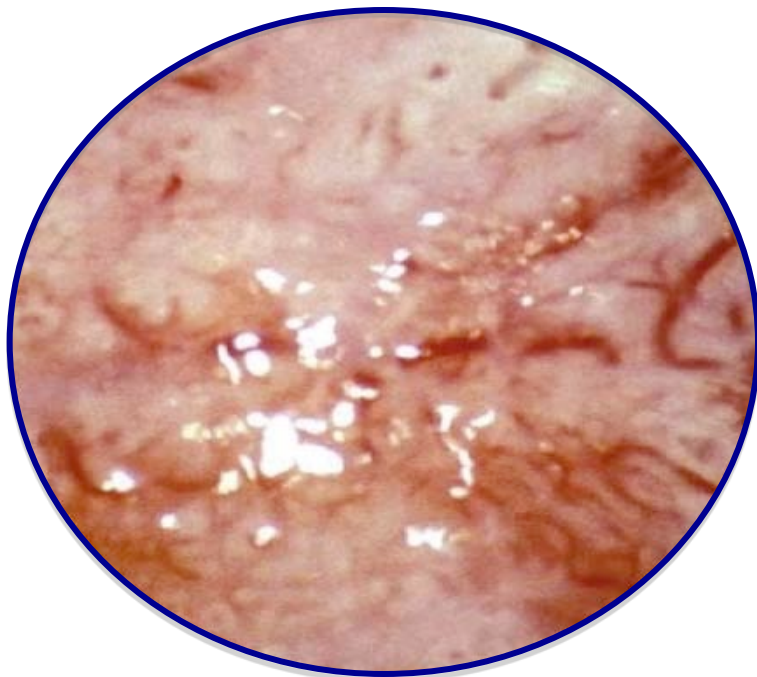
- Cisplatin 50 mg/m<sup>2</sup> plus paclitaxel 135 mg/m<sup>2</sup> standard therapy
  - Median OS ≤12 mos
- Majority of patients with recurrent cervical cancer treated with cisplatin-based chemoradiation for locally advanced disease (1999+)
  - Concern for acquired drug resistance making platinum-based therapies less effective at recurrence
- GOG 204 (2009)
  - Phase 3 randomized trial of 4 platinum-based chemotherapy doublets
  - Closed for futility
- New therapeutic options needed
  - ? Non-platinum chemotherapy doublets
  - ? Anti-angiogenesis therapy

Tewari KS, Monk BJ. Curr Oncol Rep 2005;7:419-34.  
Monk BJ, Tewari KS, Koh WJ. J Clin Oncol 2007;25:2952-65.  
Tewari KS, Monk BJ. Onkologie 2008;32:552-4.  
Monk BJ et al. J Clin Oncol 2009;27:4649-55.

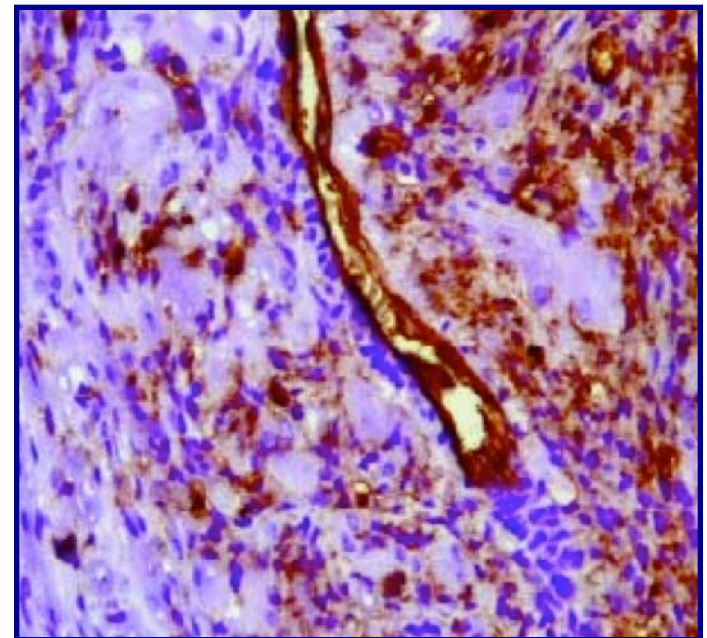
Tewari KS. Semin Oncol 2009;36:170-80.  
Tewari KS, Monk BJ. Clin Adv Hematol Oncol 2010;8:108-15.  
Tewari KS. Am J Hematol Oncol 2010;9:31-4.  
Tewari KS. Clin Ov Cancer 2011;4:90-3.

# Angiogenesis In Cervical Cancer

- Accumulating evidence supports the concept that angiogenesis plays a central role in cervical carcinogenesis and disease progression



Atypical vessels on colposcopy



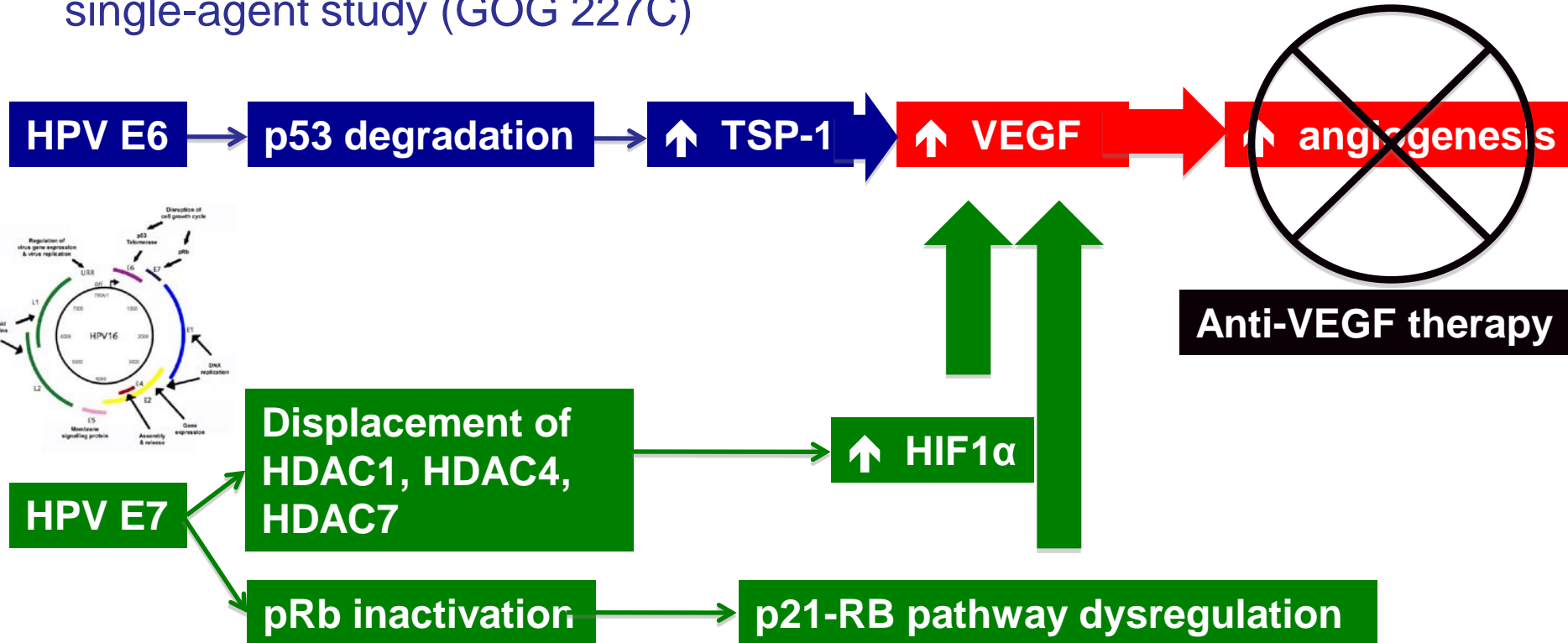
CD31 – Intratumoral microvessel density

Tewari KS, Monk BJ. Invasive Cervical Cancer. In: [Clinical Gynecologic Oncology](#), 8<sup>th</sup> ed. DiSaia PJ, Creasman WT (eds). Mosby, 2012.

# GOG 240 Hypothesis: Mechanistic

## Tumor Hypoxia and Viral Oncogenes Drive Angiogenesis

- Bevacizumab activity in cervical cancer was demonstrated in a phase 2 single-agent study (GOG 227C)



Tewari KS, et al. Gynecol Oncol 2000;77:137-48.  
 Monk BJ, et al. J Clin Oncol. 2009;27(7):1069-74.  
<http://www.microbiologybytes.com/virology/Papillomaviruses.html>

# GOG 240: Schema

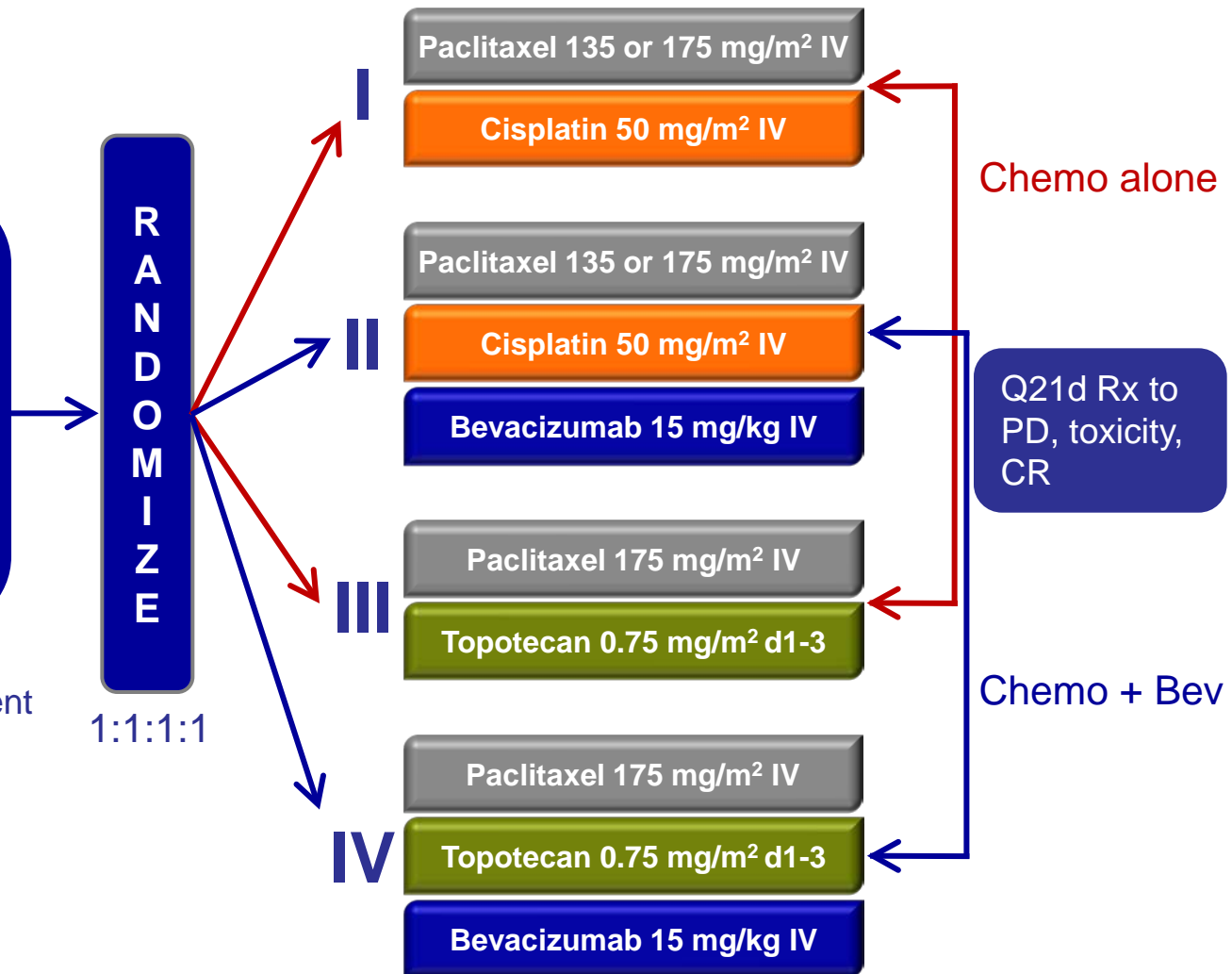
## Carcinoma of the cervix

- Primary stage IVB
  - Recurrent/persistent
  - Measureable disease
  - GOG PS 0-1
  - No prior chemotherapy for recurrence
- (N=452)

### Stratification factors:

- Stage IVB vs recurrent/persistent disease
- Performance status
- Prior cisplatin Rx as radiation-sensitizer

Activated: 4/6/09  
Closed to accrual: 1/3/12



KS Tewari (study chair). [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) Identifier: NCT00803062.

# GOG 240: Objectives

- Primary end points to determine
  - If adding bevacizumab to chemotherapy improves OS
  - If a non-platinum doublet (topotecan + paclitaxel) improves OS
  - The tolerability of the four regimens (adverse events by CTCAE v3 and v4)
- Secondary end points to determine
  - Impact of bevacizumab and non-platinum doublet on progression-free survival (PFS) and overall response rate (ORR) by RECIST v1.0
- Exploratory end points
  - Impact on Health-Related Quality of Life (HRQoL):
    - Functional Assessment of Cancer Therapy – Cervix Ca Trial Outcome Index (FACT-Cx TOI)
  - Data not included in current presentation
    - Additional HRQoL: FACT/GOG-Ntx (neuropathy), BPI (Brief Pain Inventory)
    - Prospective validation of pooled clinical prognostic factors from prior phase 3 trials
    - Prevalence and impact of nicotine dependence on OS and PFS
    - Circulating tumor cells and VEGF isoform expression

KS Tewari (study chair). [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) Identifier: NCT00803062.

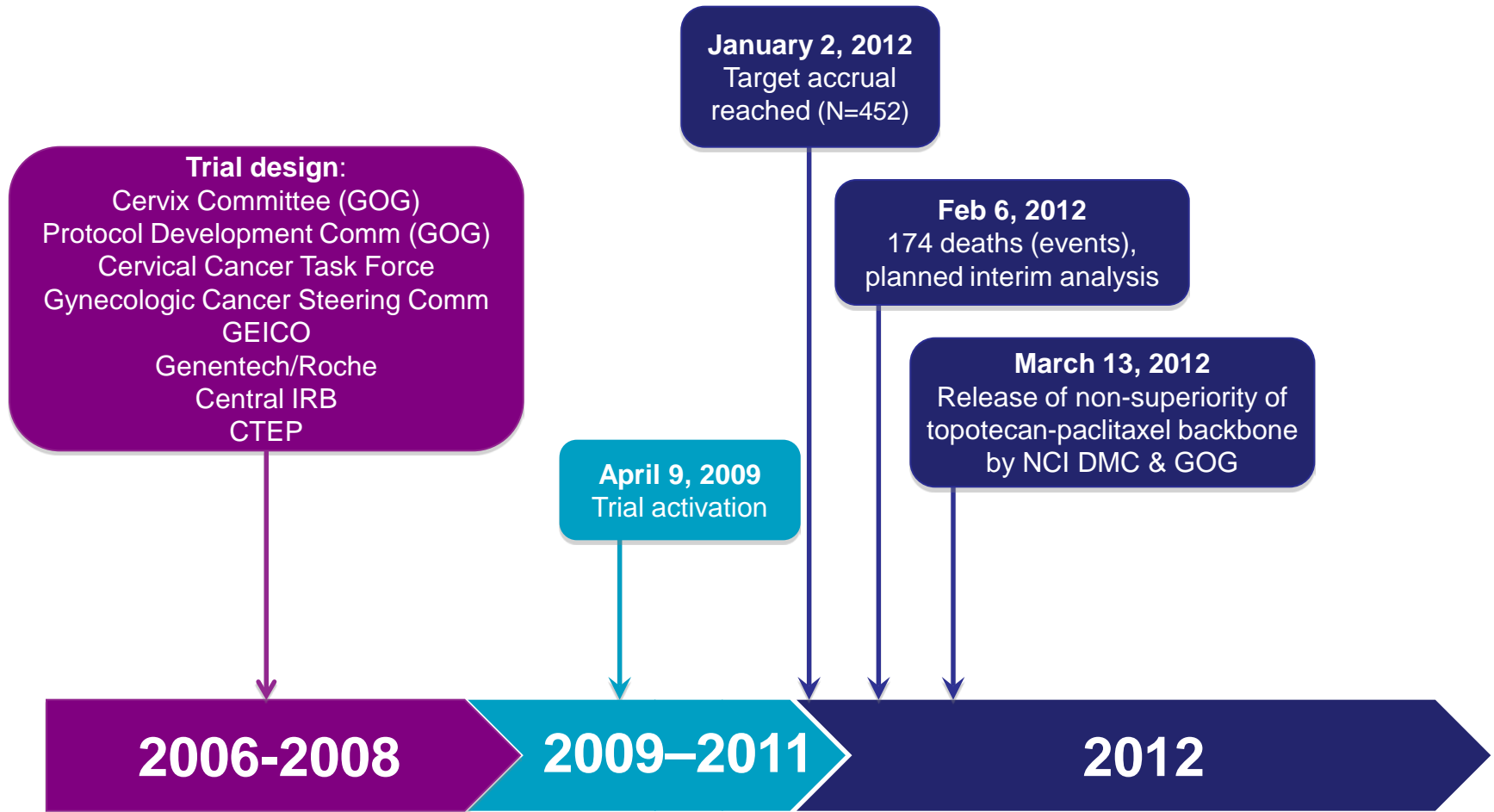
# GOG 240: Statistical Considerations

- Phase 3 open-label study
  - 2x2 factorial design with two primary independent hypotheses tested
  - The impact of non-platinum doublets compared with a platinum doublet
  - The impact of the addition of anti-angiogenic therapy to chemotherapy
- Assumptions for the primary end point of OS
  - Sample size=450
  - Assumes no evidence of interaction between factors
  - 346 deaths required to detect a reduction in the hazard of death by 30% by the addition of either factor with a power of 90%
  - 5% alpha for each of the two primary hypothesis tests (2.5% ea.)
  - Goal to increase median OS from 12 mos to 16 mos
- Pre-planned interim analysis after 173 events to determine futility or superiority of either experimental factor
- Two sequential two-stage toxicity analyses to monitor for unacceptable toxicity in the experimental arms

KS Tewari (study chair). [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) Identifier: NCT00803062.

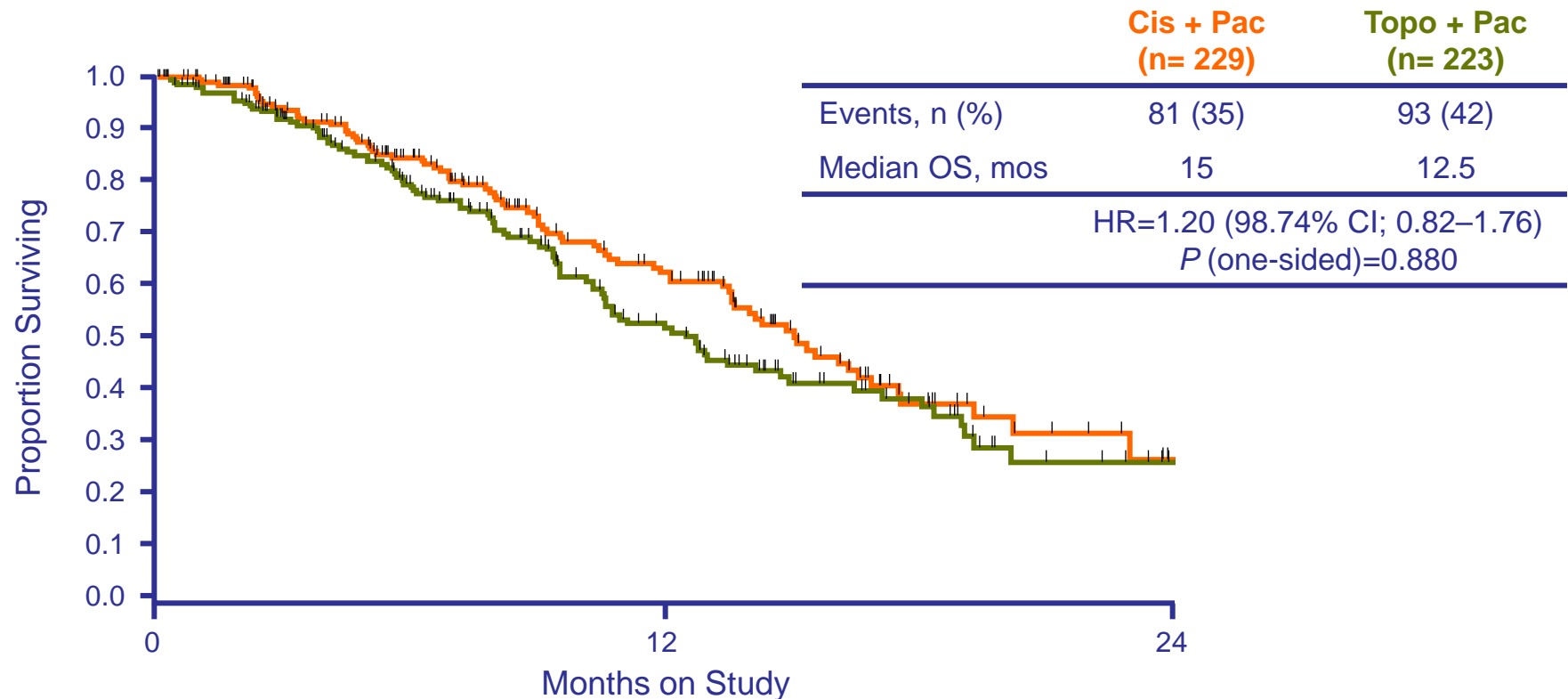


# GOG 240: Study Timeline, Part 1



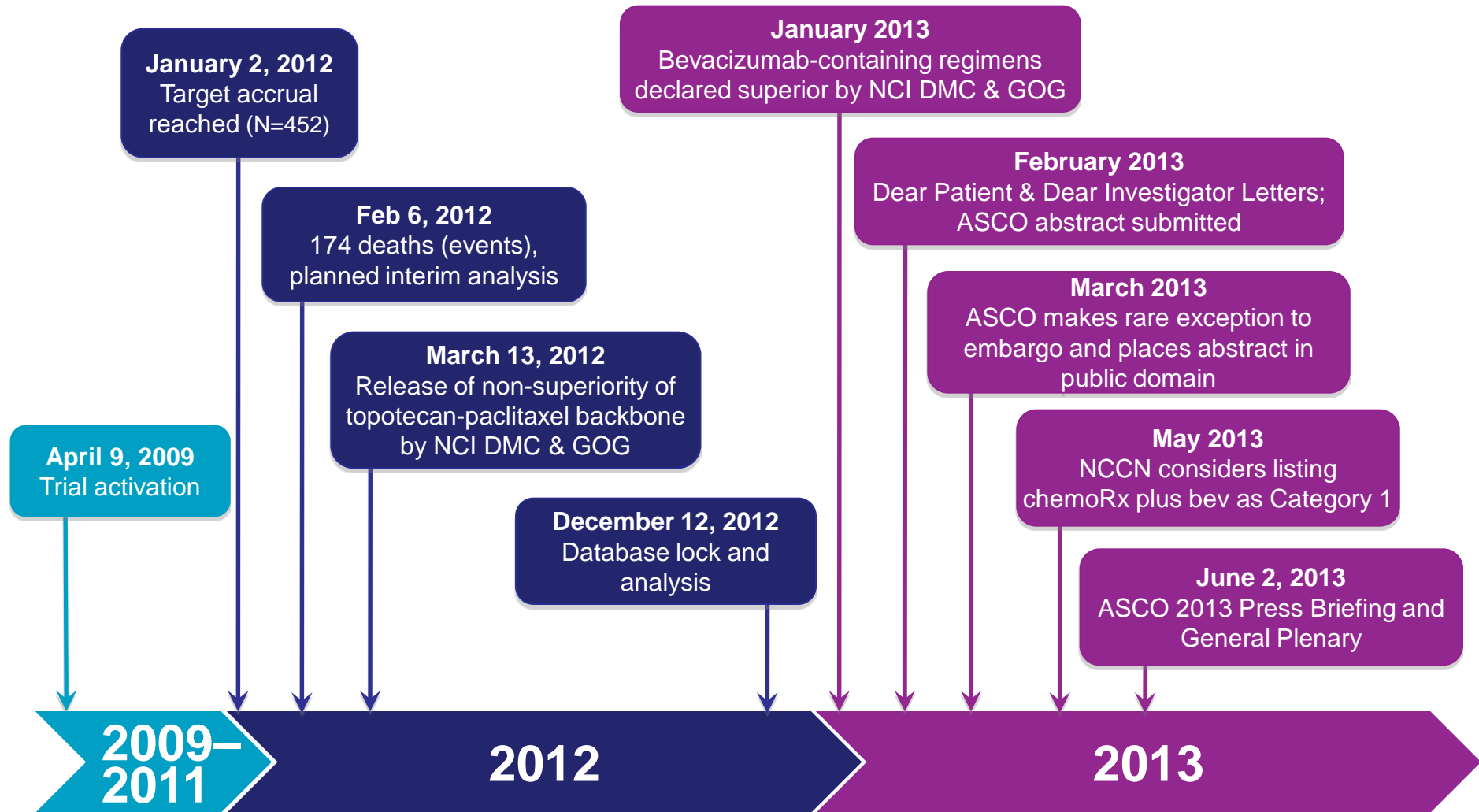
# GOG 240: Interim Analysis

- Feb 2012 study results released on non-platinum doublet vs platinum-doublet
  - Topotecan + paclitaxel shown to not be superior or inferior to cisplatin + paclitaxel



Tewari KS et al. Presented at the 2013 SGO Annual Meeting on Women’s Cancer. Abstract #1.

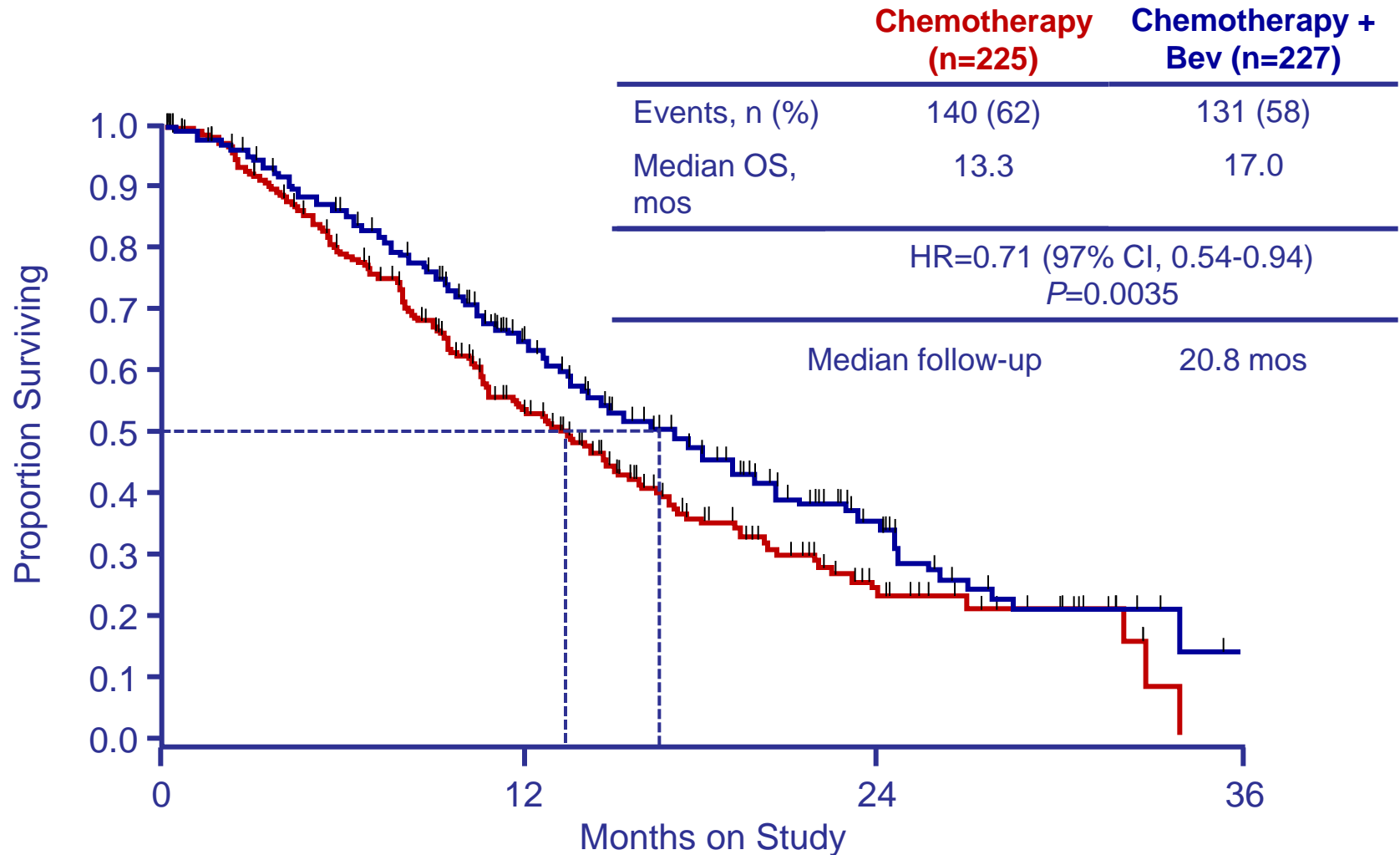
# GOG 240: Study Timeline, Part 2



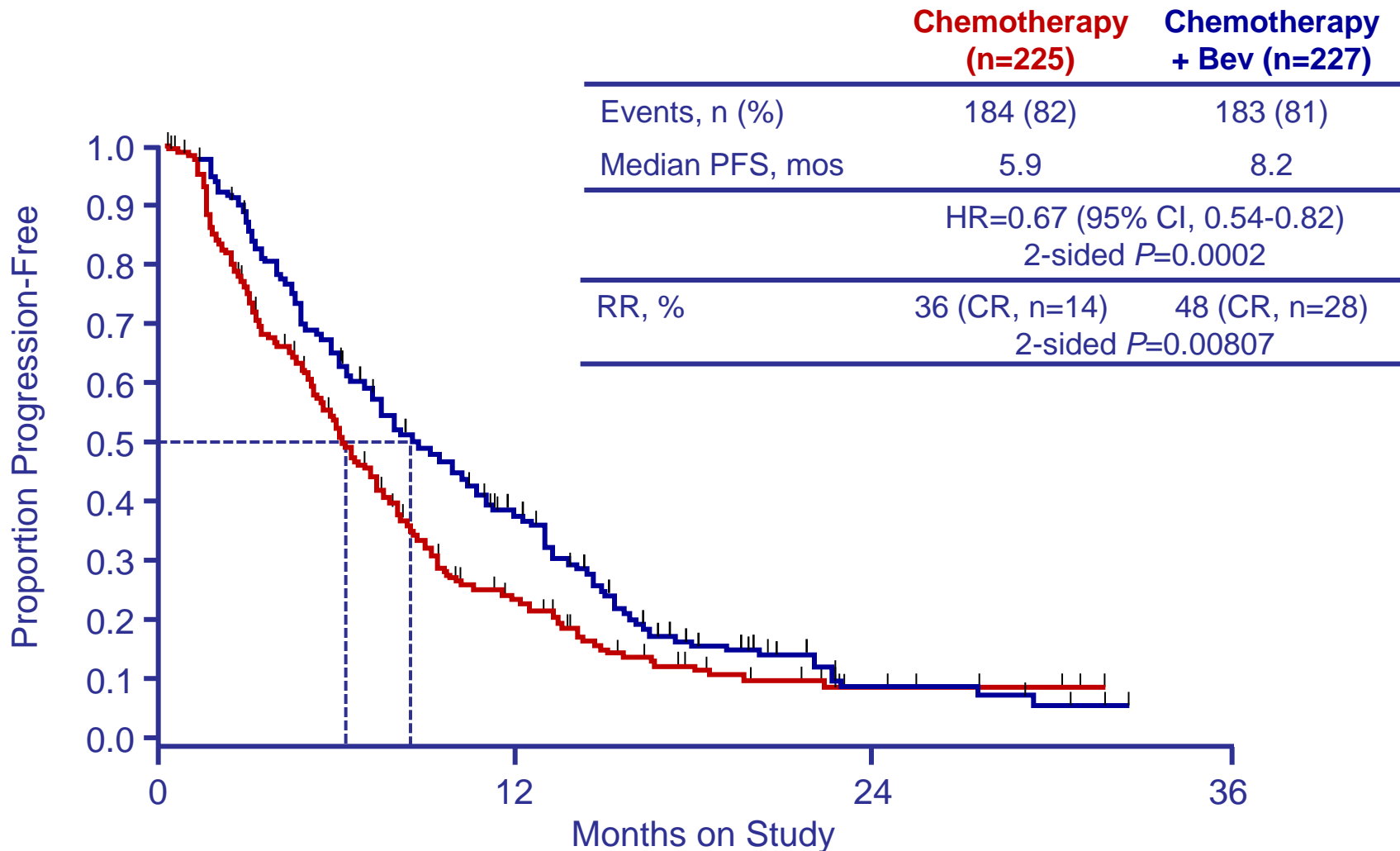
# GOG 240: Demographics & Baseline Characteristics

Characteristic	Chemo Alone (n=225), %	Chemo + Bev (n=227), %
Median age, years (range)	46 (20–83)	48 (22–85)
Histology, %		
Squamous	68	70
AdenoCa, unspec.	20	19
Race, %		
White	80	75
African American	11	16
Asian	3	5
Pacific Islander	0	0
Stage of disease, %		
Recurrent	73	70
Persistent	10	12
Advanced	16	17
Performance status, %		
0	58	58
1	42	42
Prior platinum, %	74	75
Pelvic disease, %	53	54

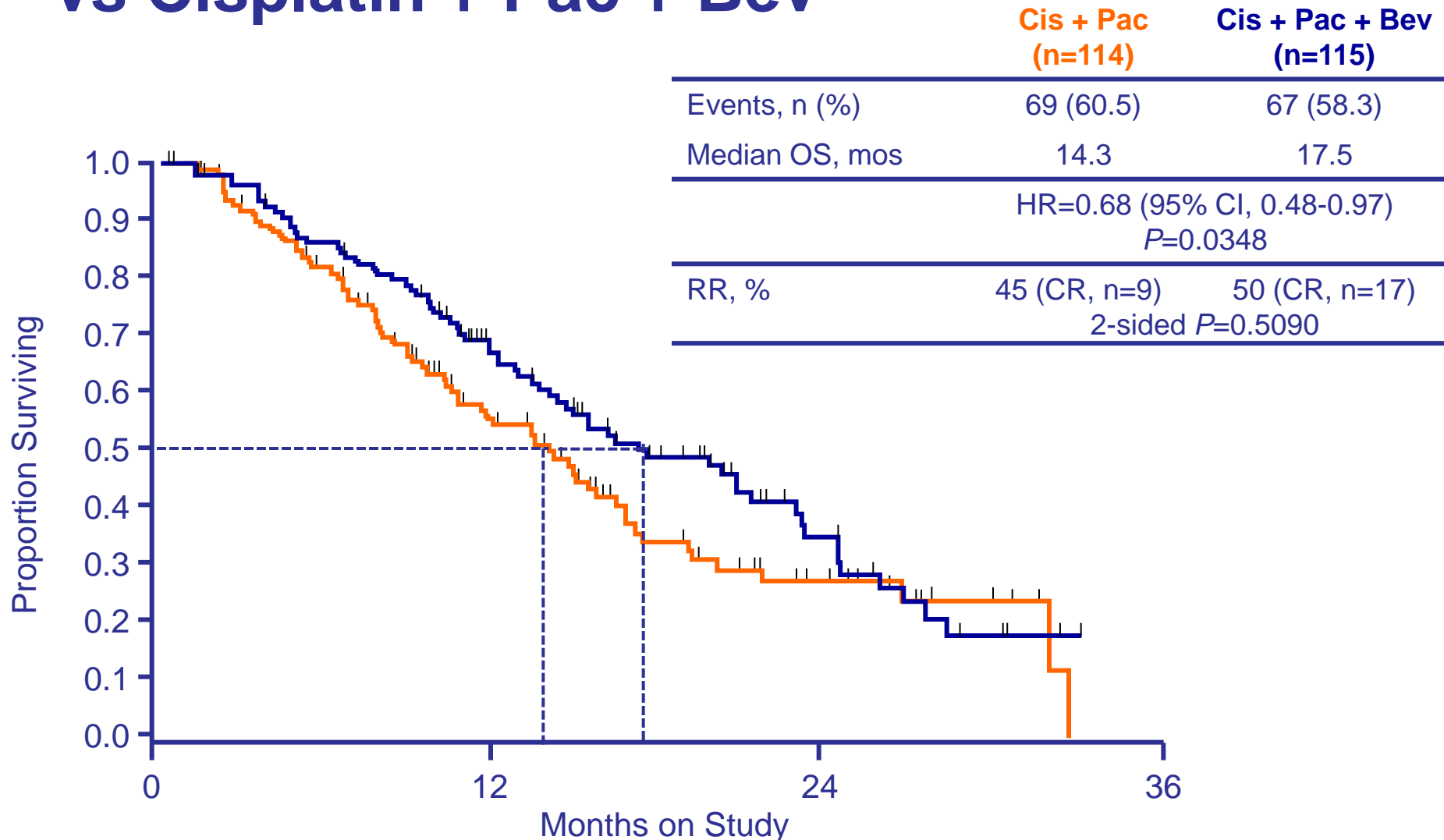
# GOG 240: OS for Chemo vs Chemo + Bev



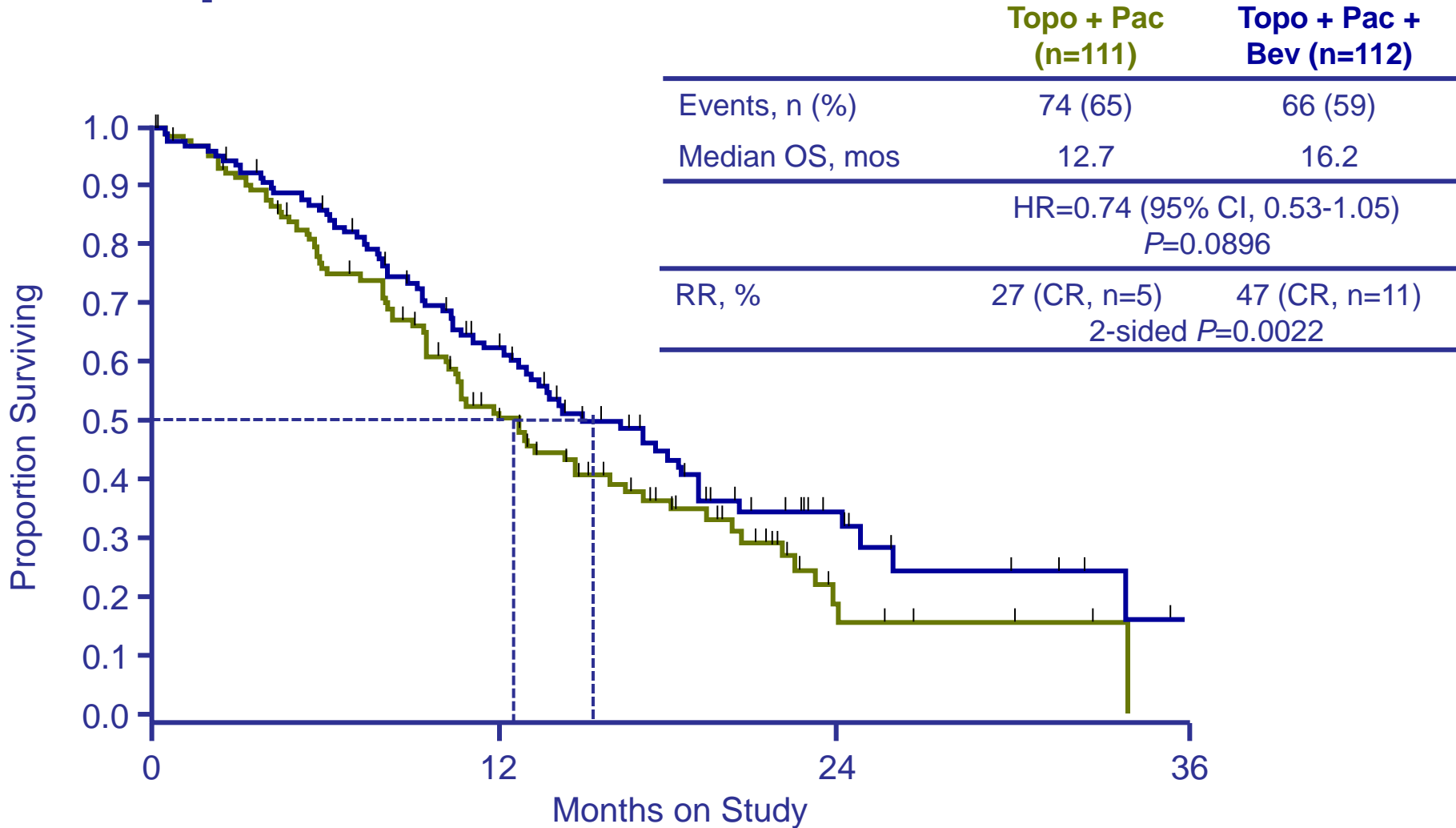
# GOG 240: PFS for Chemo vs Chemo + Bev



# GOG 240: OS for Cisplatin + Paclitaxel vs Cisplatin + Pac + Bev

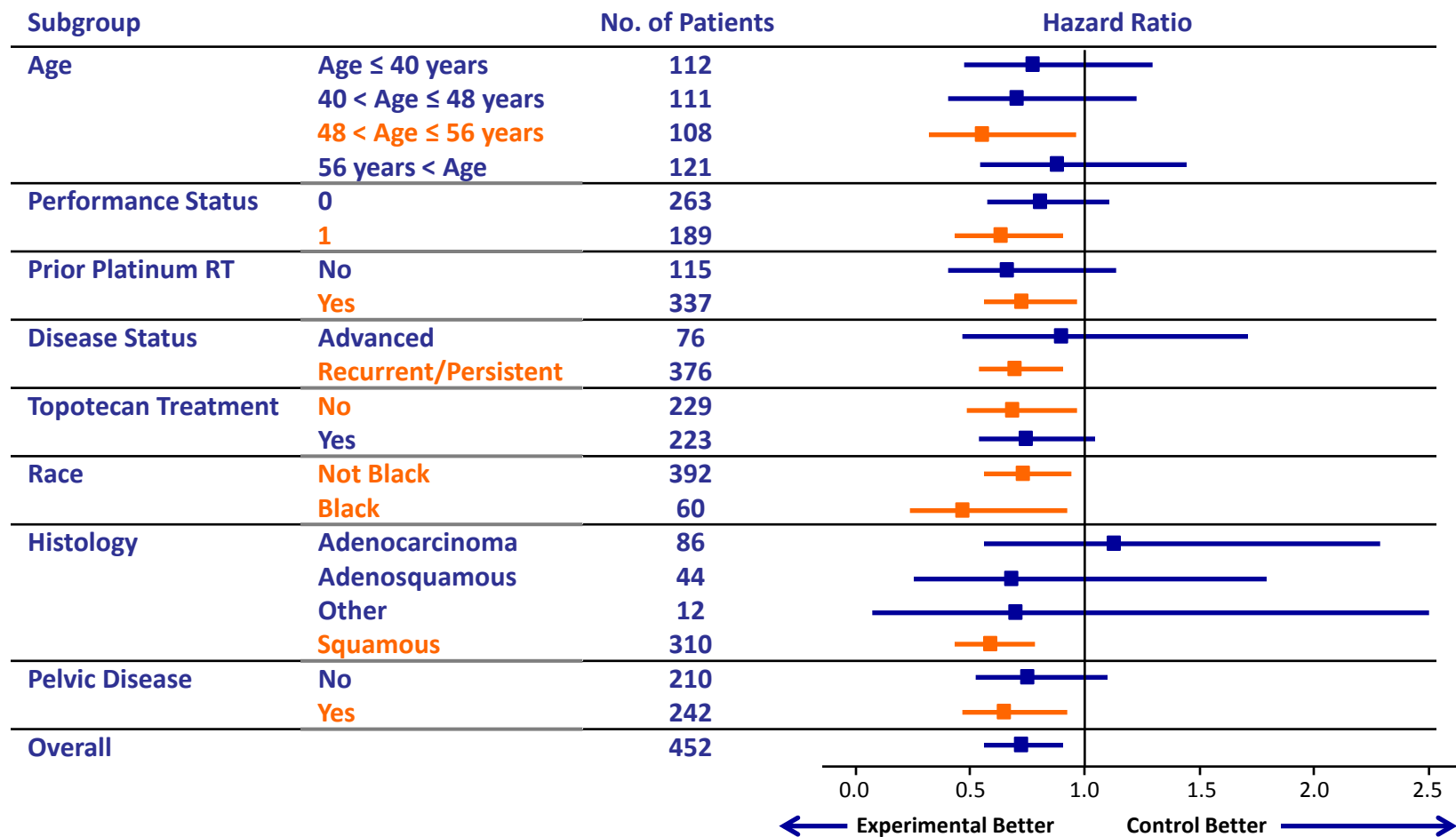


# GOG 240: OS for Topotecan + Paclitaxel vs Topotecan + Paclitaxel + Bev





# GOG 240: OS and Prognostic Factors



# GOG 240: Treatment Exposure and Specific Adverse Events

Adverse Event, n (%)	Chemo Alone (n=219)	Chemo + Bev (n=220)
Treatment cycles, median (range)	6 (0-30)	7 (0-36)
Grade 5 AE(s)	4 (1.8)	4 (1.8)
GI events, non-fistula (grade $\geq 2$ )	96 (44)	114 (52)
GI fistula (grade $\geq 3$ )*	0 (0)	7 (3)
GI perforation (grade $\geq 3$ )	0 (0)	5 (2)
GU fistula (grade $\geq 3$ )*	1 (0)	6 (2)
Hypertension (grade $\geq 2$ )*	4 (2)	54 (25)
Proteinuria (grade $\geq 3$ )	0 (0)	4 (2)
Pain (grade $\geq 2$ )	62 (28)	71 (32)
Neutropenia (grade $\geq 4$ )*	57 (26)	78 (35)
Febrile neutropenia (grade $\geq 3$ )	12 (5)	12 (5)
Thromboembolism (grade $\geq 3$ )*	3 (1)	18 (8)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade $\geq 3$ )	1 (0)	4 (1)
GU (grade $\geq 3$ )	1 (0)	6 (3)

\*p<0.05

# GOG 240: Health Related Quality of Life

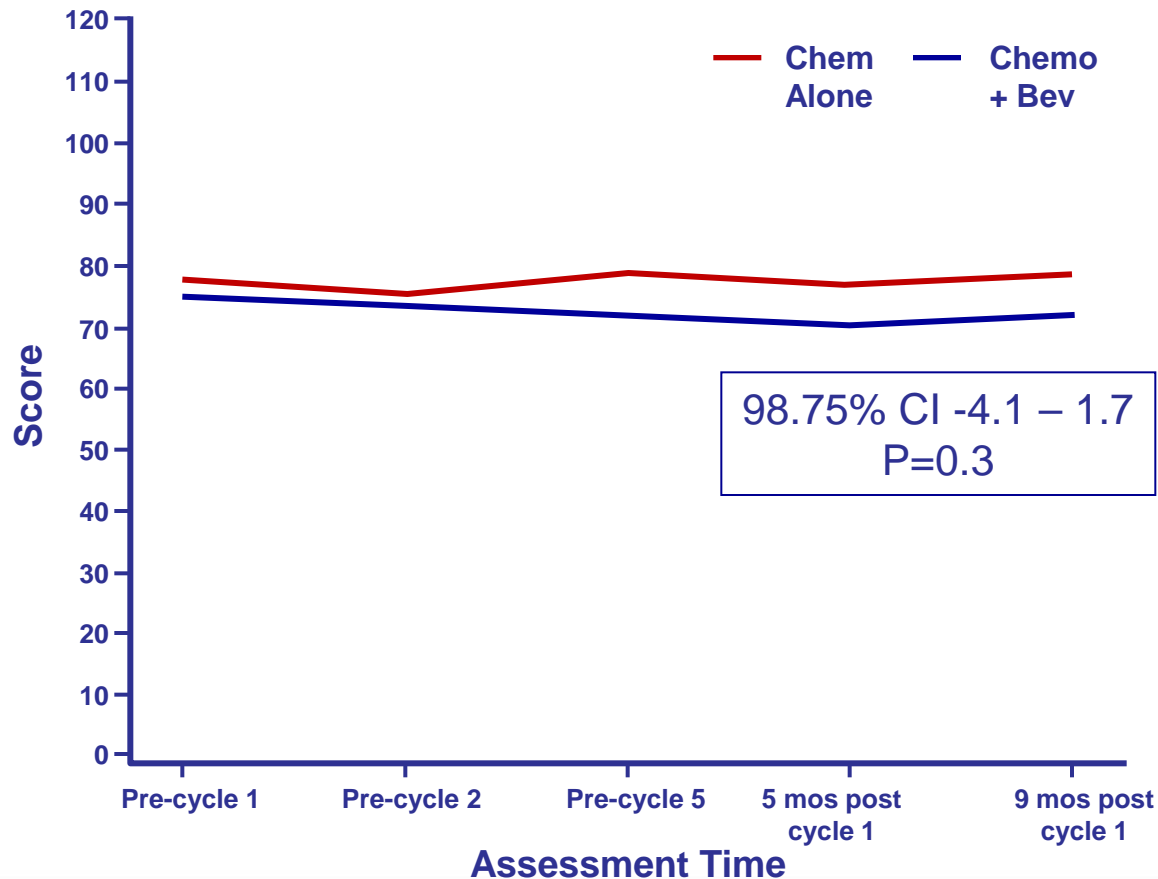
- FACT for Cervical Cancer – Trial Outcome Index
  - Physical well-being (7 items)
  - Functional well-being (7 items)
  - Cervix Cancer subscale (15 items)
  - Score range: 0-116 points
  - Clinically meaningful change: 4-5 points
- Compliance with completion of HRQoL questionnaires ranged from 96% pre-cycle 1 to 63% 9 mos post-cycle 1 and was balanced across arms

FACT-Cx TOI Score	Chemo Alone	Chemo + Bev	Difference	98.75% CI
Pre-cycle 1	77.9	75.8	-2.17	-6.43–2.09
Pre-cycle 2	77.4	76.9	-0.47	-3.59–2.64
Pre-cycle 5	77.6	74.7	-2.95	-6.81–0.90
6 mos post-cycle 1	74.0	71.2	-2.84	-7.40–1.73
9 mos post-cycle 1	74.5	72.7	-1.80	-7.10–3.50

Yost KJ, Eton DT. Eval Health Prof 2005;28:172-91.

# GOG 240: Mean FACT-Cx TOI

- Patients receiving bevacizumab reported 1.2 points lower on average



# GOG 240: Conclusions

- Bevacizumab plus chemotherapy significantly improves OS in stage IVB, recurrent or persistent cervical carcinoma
  - Nearly 4-month improvement in OS is clinically significant
  - Increase in median PFS and ORR are also demonstrated
  - Cisplatin + paclitaxel arm is current standard of care and did not underperform
  - Benefit seen even when recurrent disease is in irradiated pelvis
- Bevacizumab treatment is associated with a higher rate of AEs
  - 3–8% rate of known bevacizumab-related AEs
- The improvement in OS with bevacizumab treatment was not accompanied by a decrease in HRQoL
- First targeted agent to improve OS in a gynecologic cancer

# GOG 240: Discussion – Moving Forward

- Incorporation of anti-VEGF therapy for primary treatment of locally advanced disease
- Future studies in GOG 240 patient population
  - Dose determination of bevacizumab
  - Cost-effectiveness studies
  - Other classes of anti-angiogenic agents
    - VEGF-dependent (eg, pazopanib, sorafenib)
    - Non-VEGF-dependent (Ang 1/Ang 2 pathway inhibitors)
  - Vascular disrupting agents
  - Combined anti-angiogenesis and E7-based immunotherapy

Tewari KS, Monk BJ. Gynecol Oncol 2011;122:209-12.

Tewari KS. Int J Gynecol Cancer 2012;22:1634-9.

# GOG 240: Study Team and Support

## Study Design

- MW Sill (Statistician)
- BJ Monk (GOG Cervix Cancer Committee Chair)
- HJ Long III (Med Onc) (1946-2013)

## Co-Authors

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- A Oaknin (GEICO)
- RT Penson (HRQoL)
- H Michael (Pathology)

## Co-Investigators

- MJ Birrer, H Lankes, KM Darcy, RA Burger (Translational)
- DH Moore (Prognostic factors)
- S Waggoner (Smoking)

## Genentech/Roche

- K Look, A Husain, A Cannon

## GOG

- PJ DiSaia (Group Chair)
- MF Brady, F Stehman
- L Reese, A Kuras
- M Colahan, K Neff

## CTEP/NCI

- J Zujewski, T Trimble
- J Abrams, M Mooney
- L Rubenstein

## UCI

- J Smith (Study Nurse)

# GOG 240: Acknowledgements

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Aultman Health Foundation  
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Memorial Baylor All Saints Medical Center  
Baystate Medical Center  
Billings Clinic  
Black Hills OB/GYN  
Brooke Army Medical Center  
Broward General Medical Center  
Bryn Mawr Hospital  
Cancer Center of Kansas - Dodge City  
Cancer Center of Kansas - Wichita  
Cancer Institute of New Jersey  
Carilion Clinic Gynecological Oncology  
Carolinas Medical Center  
Central Georgia Gynecologic Oncology  
Christiana Healthcare Services CCOP  
City of Hope National Medical Center  
Cleveland Clinic Cancer Center/Fairview Hospital  
Cleveland Clinic Foundation  
Columbus Cancer Council/Ohio State  
Cooper Hospital/University Medical Center  
Dana-Farber Cancer Institute  
Dartmouth-Hitchcock Medical Center  
Fairview Ridges Hospital

Florida Gynecologic Oncology  
Florida Hospital Cancer Institute  
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Hillcrest Hospital  
Hope, A Women's Cancer Center  
Hospital Universitario de Girona Dr. Josep Trueta  
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Hospital Vall d'Hebron  
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Lehigh Valley Hospital  
Lester E. Cox Medical Center

Long Island Jewish Medical Center  
Louisiana State University Health Sciences Center  
Lutheran General Cancer Care Center  
Lyndon Baines Johnson General Hospital  
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M.D. Anderson Cancer Center  
Maine Medical Center  
Marshfield CCOP  
Mayo Clinic in Florida  
Mayo Clinic  
Medical College of Wisconsin  
Medical University of South Carolina  
MedStar Franklin Square Medical Center/Weinberg Cancer Institute  
Meharry Medical College Minority Based CCOP  
Memorial Health University Medical Center  
Memorial Healthcare System Joe DiMaggio Children's Hospital  
Memorial Medical Center of Southern Illinois University  
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Minnesota Oncology and Hematology, P.A.  
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# GOG 240: Acknowledgements, con't

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Penrose St. Francis Healthcare  
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Schwartz Gynecologic Oncology  
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St. Joseph Hospital  
St. Joseph Mercy – Oakland  
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St. Luke's Hospital  
St. Vincent Oncology Center

St. Vincent Regional Cancer CCOP  
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The Lankenau Hospital  
Tulane University School of Medicine  
Tulsa Cancer Institute-South Yale  
UCSF/Mt. Zion Cancer Center  
UMDNJ-New Jersey Medical School  
Union Hospital  
University Medical Center, Brackenridge  
University of Alabama at Birmingham  
University of Arkansas  
University of California Davis Cancer Center  
University of California Medical Center at Irvine  
University of California, San Francisco-Mt. Zion  
University of Chicago  
University of Cincinnati Medical Center  
University of Colorado-Anschutz Cancer Pavilion  
University of Iowa Hospitals and Clinics  
University of Kansas Medical Center  
University of Kentucky  
University of Maryland/Greenbaum Cancer Center

University of Massachusetts Memorial Health Care  
University of Minnesota Medical School  
University of Mississippi  
University of New Mexico Health Sciences Center  
University of North Carolina  
University of Oklahoma  
University of Pittsburgh - Hillman Cancer Center  
University of South Alabama, Mitchell Cancer Inst.  
University of Southern California  
University of Tennessee - Knoxville  
University of Texas - Galveston  
University of Virginia Health Sciences Center  
University of Wisconsin Hospital  
Utah Valley Regional Medical Center  
Valley Hospital  
Vanderbilt University Medical Center  
Virginia Commonwealth University MBCCOP  
Wake Forest University School of Medicine  
Wayne State University  
Wellmont Health System  
West Michigan Cancer Center  
Wichita CCOP  
William Beaumont Hospital CCOP  
Women and Infants Hospital  
Women's Cancer Care Associates  
Women's Cancer Center of Nevada