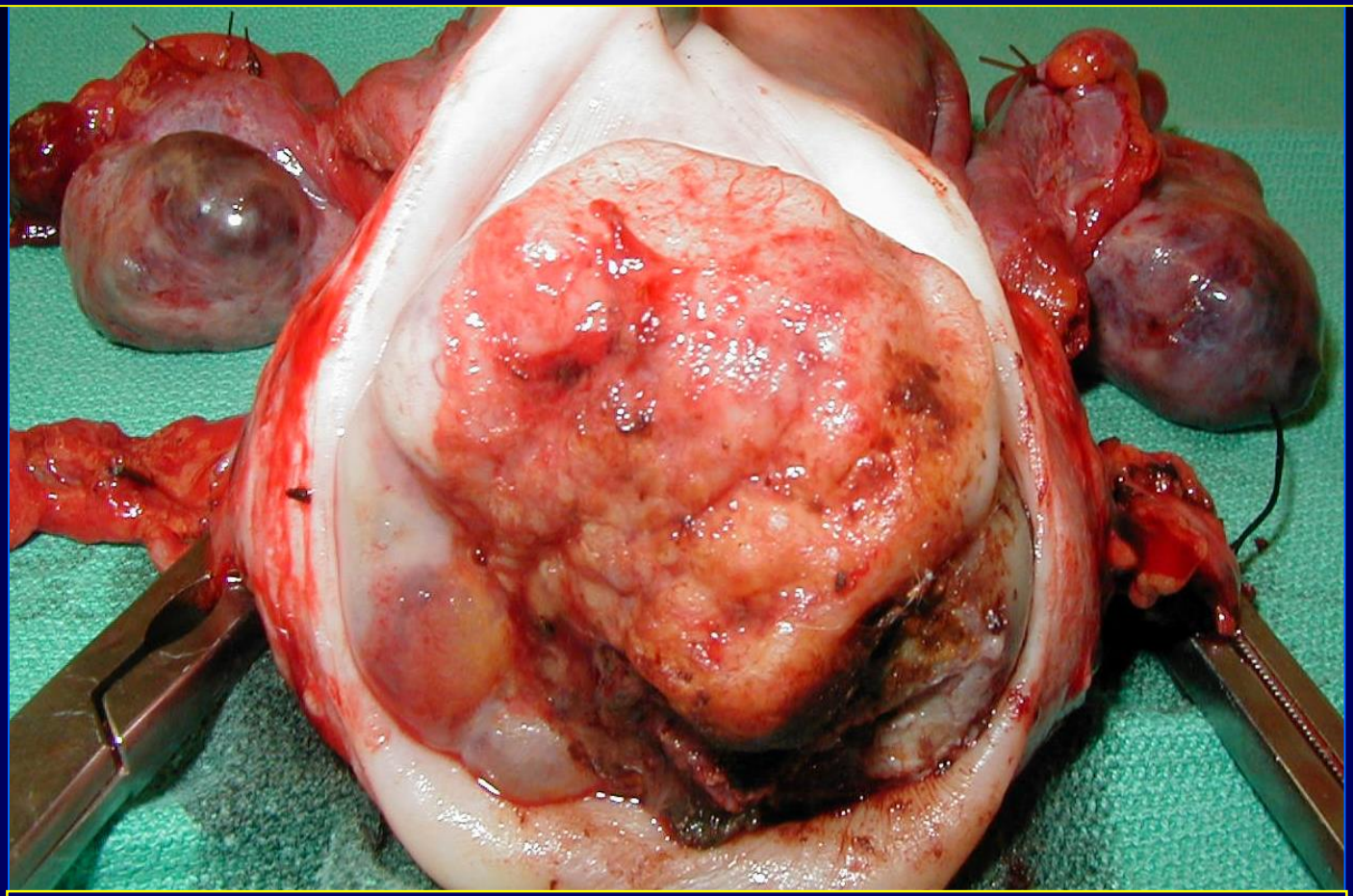
Optimal Therapies in Advanced and Recurrent Cervical Cancer



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Disclosures

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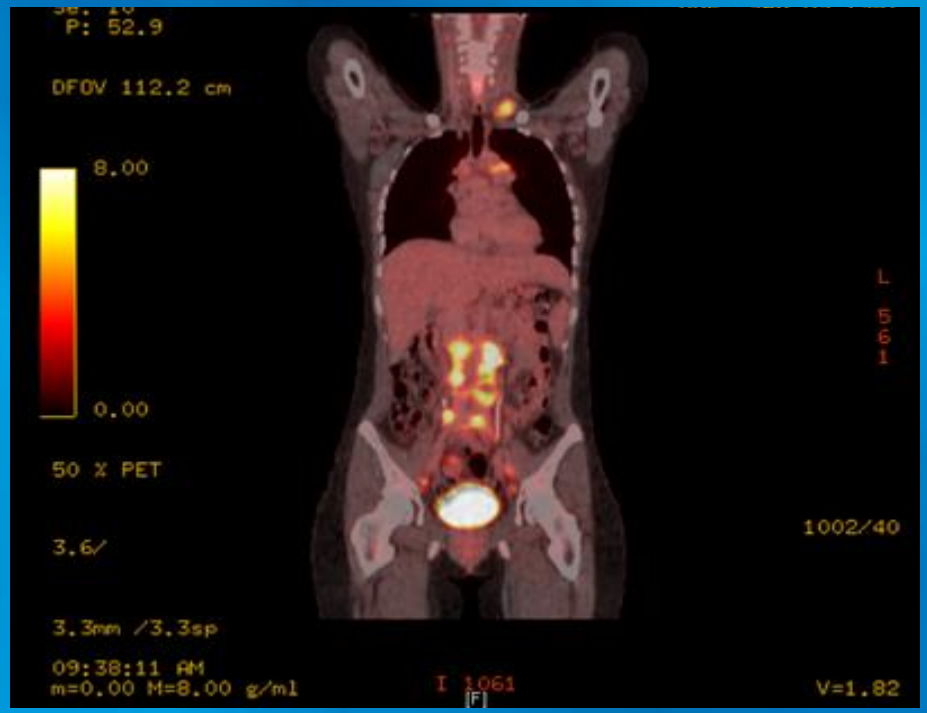
- Scientific Steering/Advisory Committee (uncompensated):
  - Amgen, AstraZeneca, Endocyte, Esperance, GSK, Genentech/Roche, Janssen, Morphotek/Easai, Merck, Medimmune, Venti,

- In September 2014 a 37-year-old woman, presented to the emergency room with odorous vaginal discharge and back pain
  - No Pap or HPV test in last 5 years
- Pre-existing conditions:
  - No other significant medical history
- Evaluation:
  - Physical examination: Necrotic fixed pelvic tumor and palpable 3-cm left supraclavicular lymph node
  - Cervix biopsy: grade 3 carcinoma
  - Fine needle aspiration of supraclavicular lymph node: grade 3 carcinoma
  - PS=0

Pretreatment PET/CT Scan



Clinical diagnosis: FIGO stage IVB

CT=computed tomography; FIGO=International Federation of Gynecology and Obstetrics; PET=positron emission tomography.

Discussion Questions

- How does one choose the chemotherapy backbone in treating metastatic cervical cancer?

- Is this the sort of patient that would benefit from bevacizumab?

Phase III Development: Advanced Stage/Recurrent Cervix Cancer

Single Agent Platinum

- GOG 43 (1987)
  - High dose (100 mg/m^2), better response, no difference in OS
- GOG 64 (1989)
  - Infusion schedule, no difference
- GOG 77 (1989)
  - Platinum analogs "probably" no better

Combination Platinum Regimens

- GOG 110 (1997)
  - Ifex improved response, no diff in OS
- GOG149 (2002)
  - Bleo adds nothing to cis/ifex
- **GOG 169 (2004)***
  - Paclitaxel improves RR, PFS but not OS
- **GOG 179 (2005)***
  - Topo/cis improves RR, PFS and OS
- GOG 204 (2009)
  - No "winner"; pac/cis better therapeutic index

***Trials spanned incorporation of platinum-based chemo-XRT**

JCOG
Japan Clinical Oncology Group
(www.jcog.jp/en/)

Cisplatin/Paclitaxel vs. Carboplatin/Paclitaxel: JCOG 0505 trial

253 pts stage IV /recurrent, ≤1 platinum Cx, no bilateral hydronephrosis

127 assigned to cisplatin-paclitaxel

Paclitaxel **135** mg/m^2 **24h** d1
Cisplatin 50 mg/m^2 2h **d2**

126 assigned to carboplatin-paclitaxel

Paclitaxel **175** mg/m^2 **3h** d1
Carboplatin AUC 5 1h **d1**

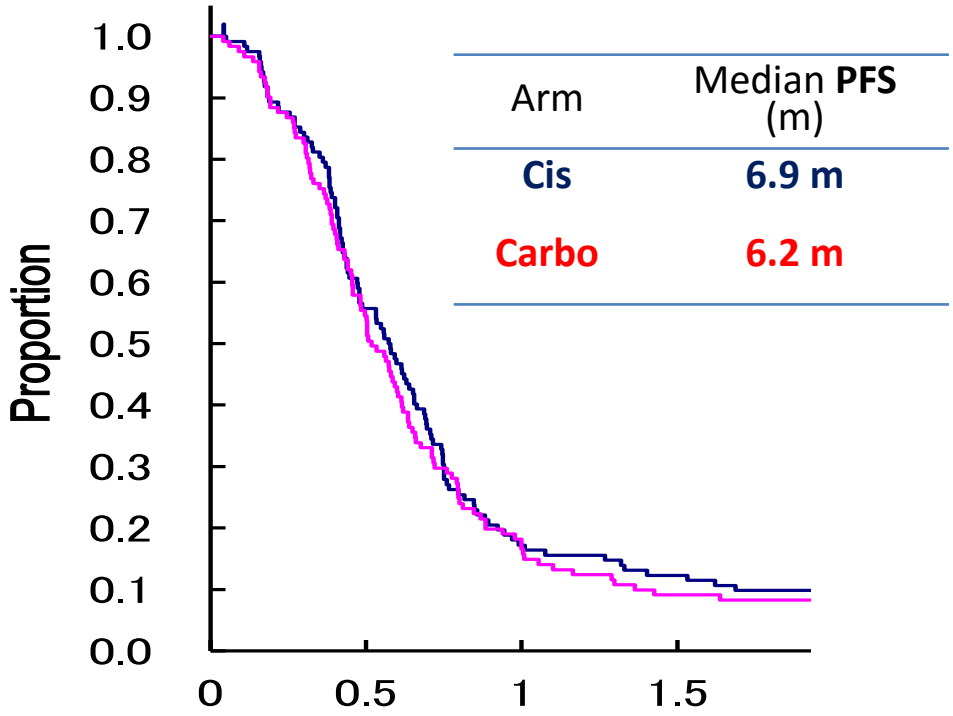
Maximum 6 cycles of treatment
until disease progression or unacceptable toxicity

Non-inferiority design (HR:1.29)

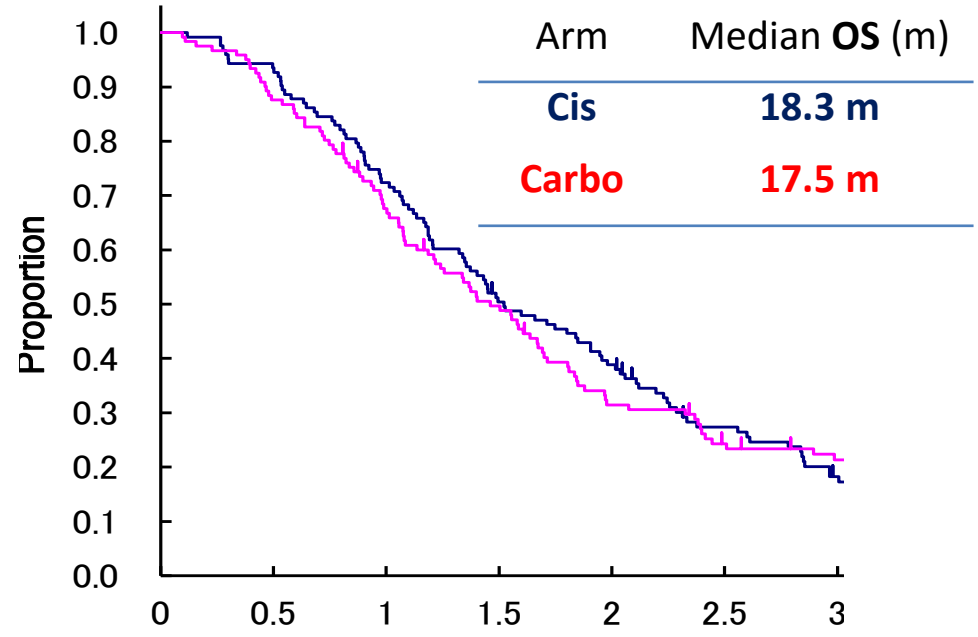
JCOG 0505 trial, Kitawaga R, J Clin Oncol 2015

JCOG
Japan Clinical Oncology Group
(www.jcog.jp/en/)

No difference in PFS and OS



Arm	Median **PFS** (m)
Cis	**6.9 m**
Carbo	**6.2 m**



Arm	Median **OS** (m)
Cis	**18.3 m**
Carbo	**17.5 m**

JCOG 0505 trial, Kitawaga R et al JCO 2015

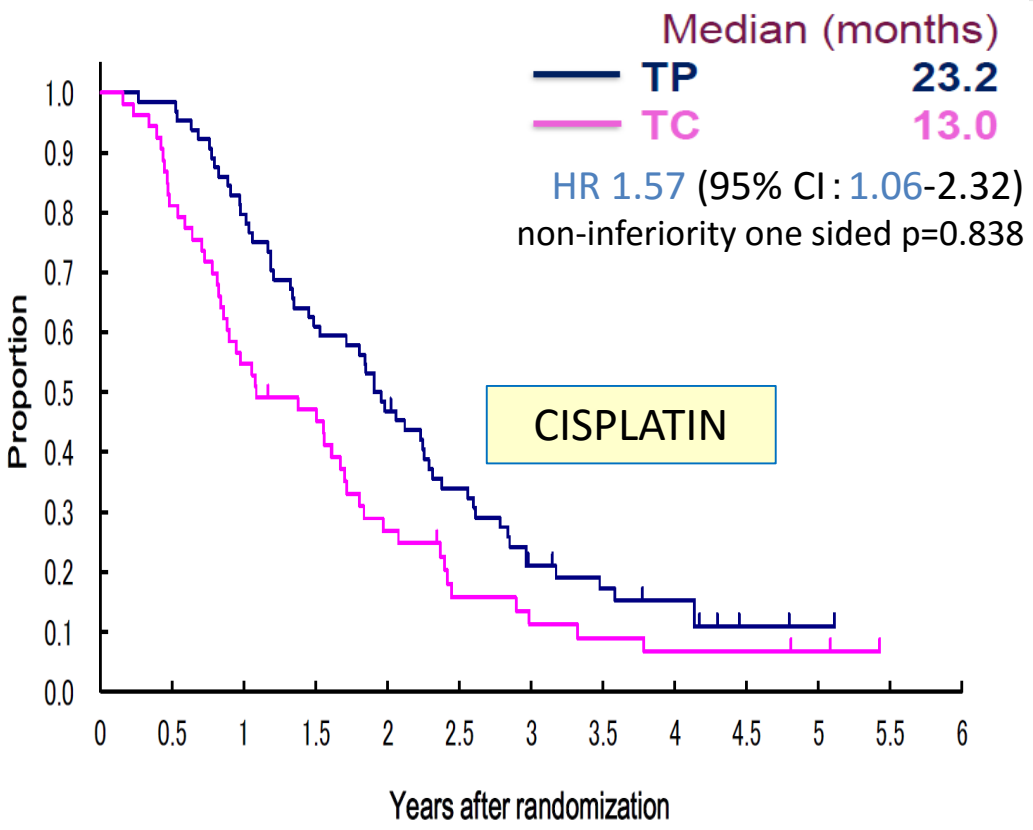
Toxicity: Balance Slightly in Favor of Carboplatin

	Grade	Cisplatin + paclitaxel	**Carboplatin** + paclitaxel	p
Neutropenia	≥3	85	76	<0.0001
Febrile neutropenia		16	7	0.03
Infection		5	5	
Platelets		3	25	
Anemia		31	44	
Fatigue	≥2	17	16	
Vomiting		30	20	
Creatinine		7	5	
Neurological		14	22	
% of non-hospitalization period		46.4	61.9	< 0.0001

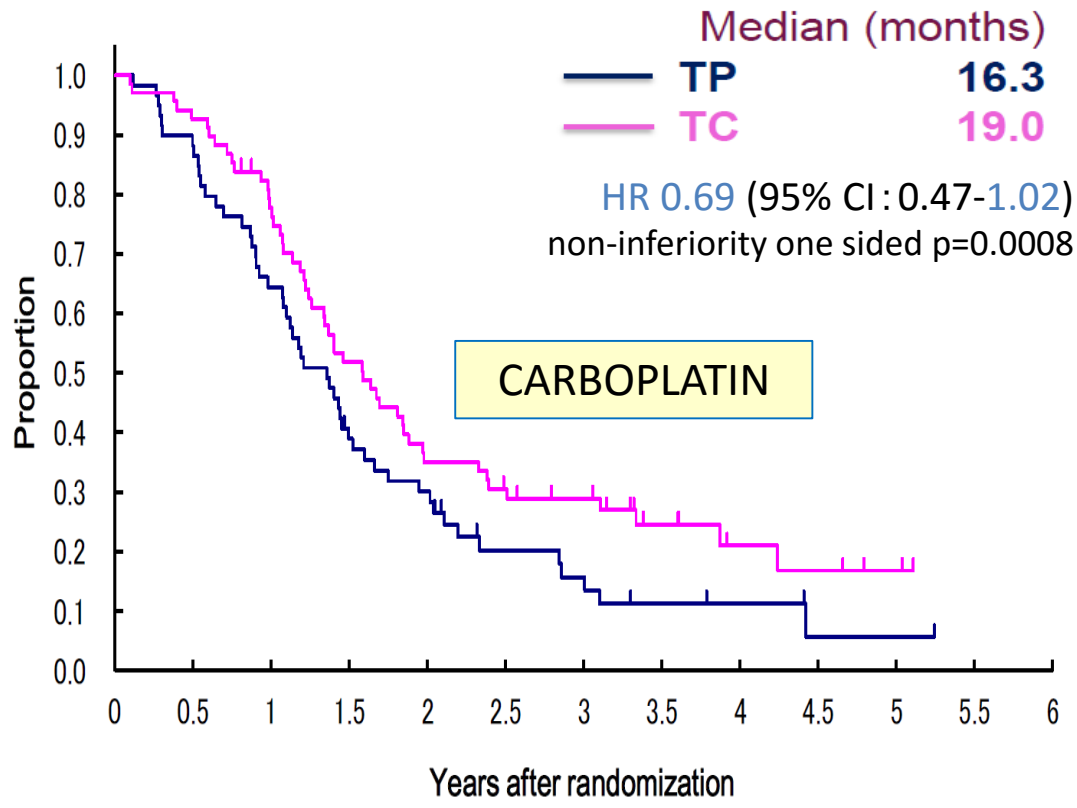
JCOG
Japan Clinical Oncology Group
(www.jcog.jp/en/)

Effects on OS of Prior Platinum

No prior cisplatin (n=117)

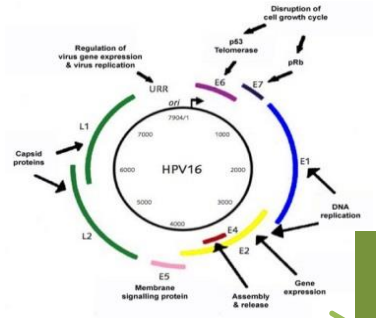


Prior cisplatin (n=127)



JCOG 0505 trial, Kitawaga R et al, JCO 2015

Tumor Hypoxia and Viral Oncogenes Drive Angiogenesis



HPV E6 → p53 degradation → ↑ TSP-1 → ↑ VEGF → ↑ angiogenesis

Anti-VEGF therapy

HPV E7 → Displacement of HDAC1, HDAC4, HDAC7 → ↑ HIF1α

HPV E7 → pRb inactivation → p21-Rb pathway dysregulation

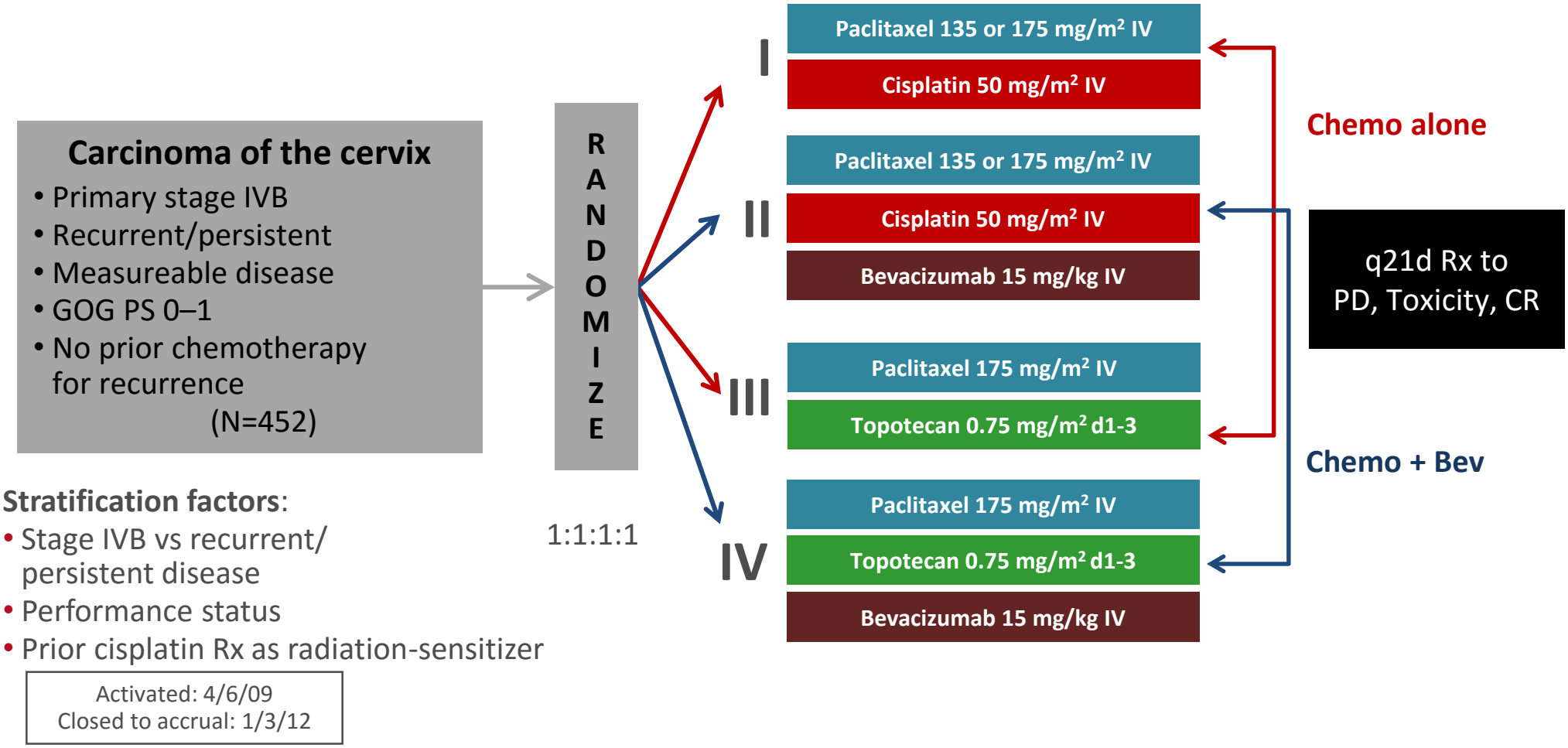
Bevacizumab activity in cervical cancer was demonstrated in a phase II single-agent study (GOG 227C)

GOG, Gynecologic Oncology Group; HDAC, histone deacetylase; HIF1α, hypoxia-inducible factor 1-alpha; HPV, human papilloma virus; pRb, retinoblastoma protein; TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor.

Tewari KS, et al. *Gynecol Oncol 2000*;77:137-48. Monk BJ, et al. *J Clin Oncol* 2009;27:1069-74.

MicrobiologyBytes. Available at: http://www.microbiologybytes.com/virology/Papillomaviruses.html. Accessed September 9, 2014.

GOG 240: Schema



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

chemo, chemotherapy; CR, complete response; GOG, Gynecologic Oncology Group; PD, progressive disease; PS, performance status; q21d, every 21 days; Rx, treatment

KS Tewari (study chair). www.ClinicalTrials.gov Identifier: NCT00803062.

Tewari NEJM 2014

GOG 240 Objectives

- Primary end points to determine
  - Primary endpoint was overall survival (OS)
    - The efficacy of the addition of bevacizumab to chemotherapy
    - The efficacy of chemotherapy doublets; platinum vs non-platinum (topotecan + paclitaxel)
  - The tolerability of the 4 regimens
- Secondary end points to determine
  - Progression-Free Survival: PFS
  - Overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors v1.0
- Exploratory end points
  - Impact on health-related quality of life (HRQoL):
    - Functional Assessment of Cancer Therapy – Cervix Ca Trial Outcome Index
  - Data not included in current presentation
    - Additional HRQoL: Gynecologic Oncology Group neurotoxicity, Brief Pain Inventory
    - Prospective validation of pooled clinical prognostic factors from prior phase III trials
    - Prevalence and impact of nicotine dependence on OS and PFS
    - Circulating tumor cells and vascular endothelial growth factor (VEGF) isoform expression

Tewari NEJM 2014

KS Tewari (study chair). www.ClinicalTrials.gov Identifier: NCT00803062.

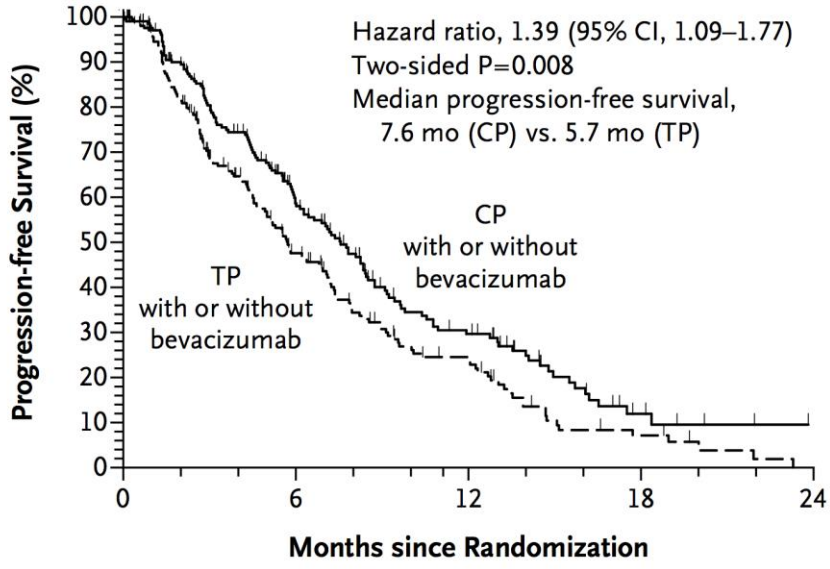
GOG 240 – Demographics & Baseline Characteristics

Characteristic	Chemo Alone (n=225), %	Chemo + Bev (n=227), %
Median age, years (range)	46 (20–83)	48 (22–85)
Histology, %		
Squamous	68	70
Adenocarcinoma, 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

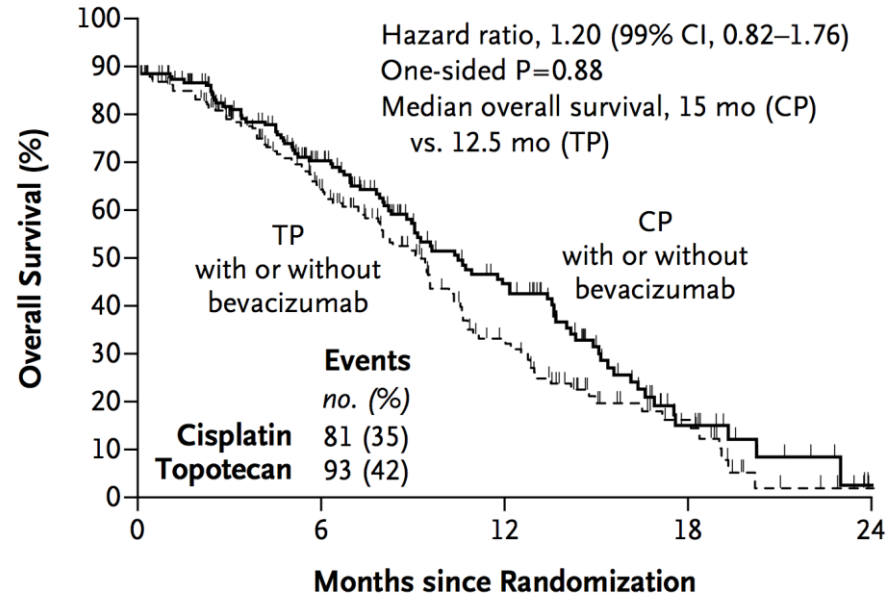
Bev, bevacizumab; chemo, chemotherapy; GOG, Gynecologic Oncology Group; unspec., unspecified.

Interim Analysis: Topo/pac vs cis/pac

	No Disease Progression	Disease Progression	Total
Cisplatin	97	132	229
Topotecan	73	150	223



No. at Risk					
CP	229	95	36	6	0
TP	223	74	29	6	0



No. at Risk					
CP	229	133	71	19	3
TP	223	122	59	23	3

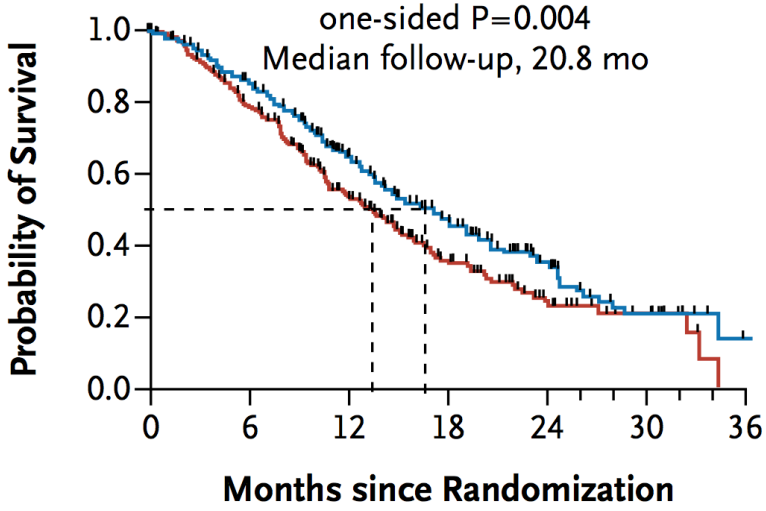
Tewari NEJM 2014

GOG-0240: Final OS/PFS

A

	Events *no. (%)*	Median Overall Survival *mo*
Chemotherapy (N=225)	140 (62)	13.3
Chemotherapy+Bev (N=227)	131 (58)	17.0

Hazard ratio, 0.71 (98% CI, 0.54–0.95); one-sided P=0.004
Median follow-up, 20.8 mo



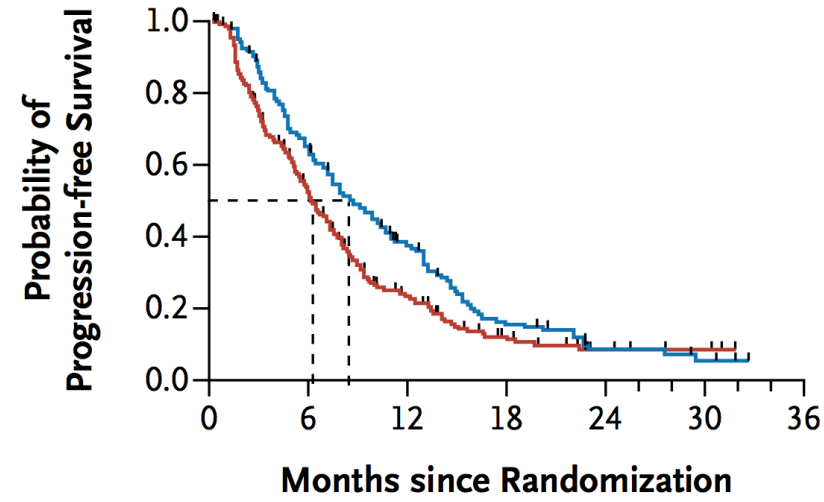
No. at Risk

Chemotherapy	225	167	94	45	17	8
Chemotherapy +bev	227	184	121	69	30	10

B

	Events *no. (%)*	Median Progression-free Survival *mo*
Chemotherapy (N=225)	184 (82)	5.9
Chemotherapy+Bev (N=227)	183 (81)	8.2

Hazard ratio, 0.67 (95% CI, 0.54–0.82); two-sided P=0.002



No. at Risk

Chemotherapy	225	103	40	14	6	3
Chemotherapy +bev	227	132	70	22	6	3

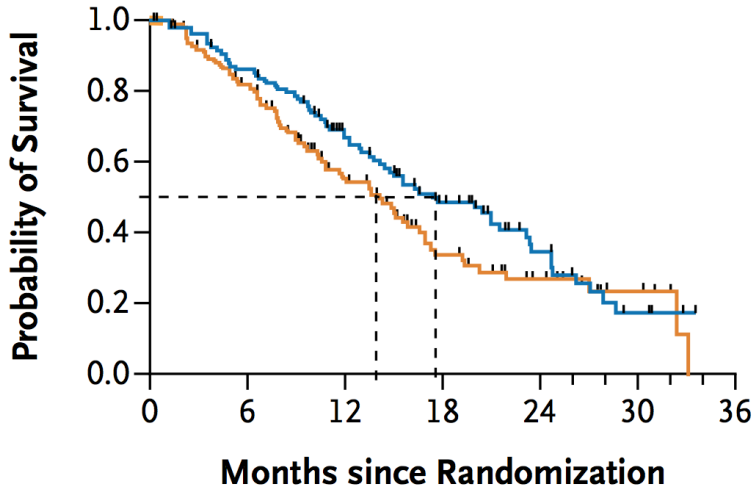
Tewari NEJM 2014

GOG-0240: Individual Arms ± Bev

C

	Events *no. (%)*	Median Overall Survival *mo*
CP (N=114)	69 (61)	14.3
CP+Bev (N=115)	66 (58)	17.5

Hazard ratio, 0.68 (95% CI, 0.48–0.97); one-sided P=0.04

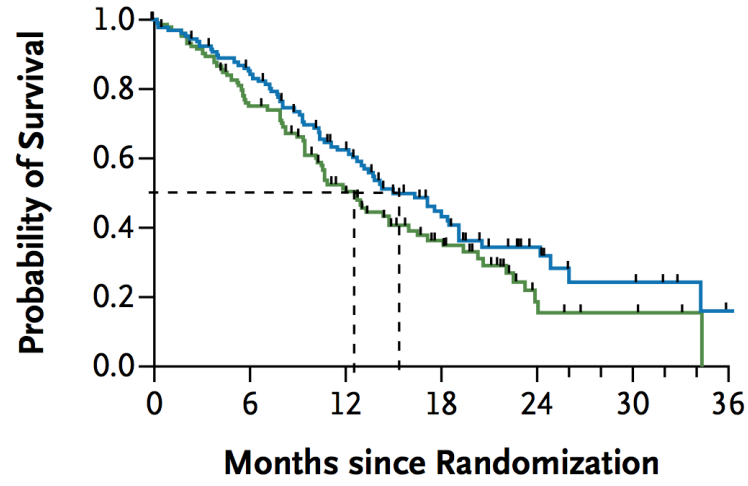


No. at Risk						
CP	114	89	50	22	12	5
CP+bev	115	94	63	37	17	5

D

	Events *no. (%)*	Median Overall Survival *mo*
TP (N=111)	71 (64)	12.7
TP+Bev (N=112)	65 (58)	16.2

Hazard ratio, 0.74 (95% CI, 0.53–1.05); one-sided P=0.09

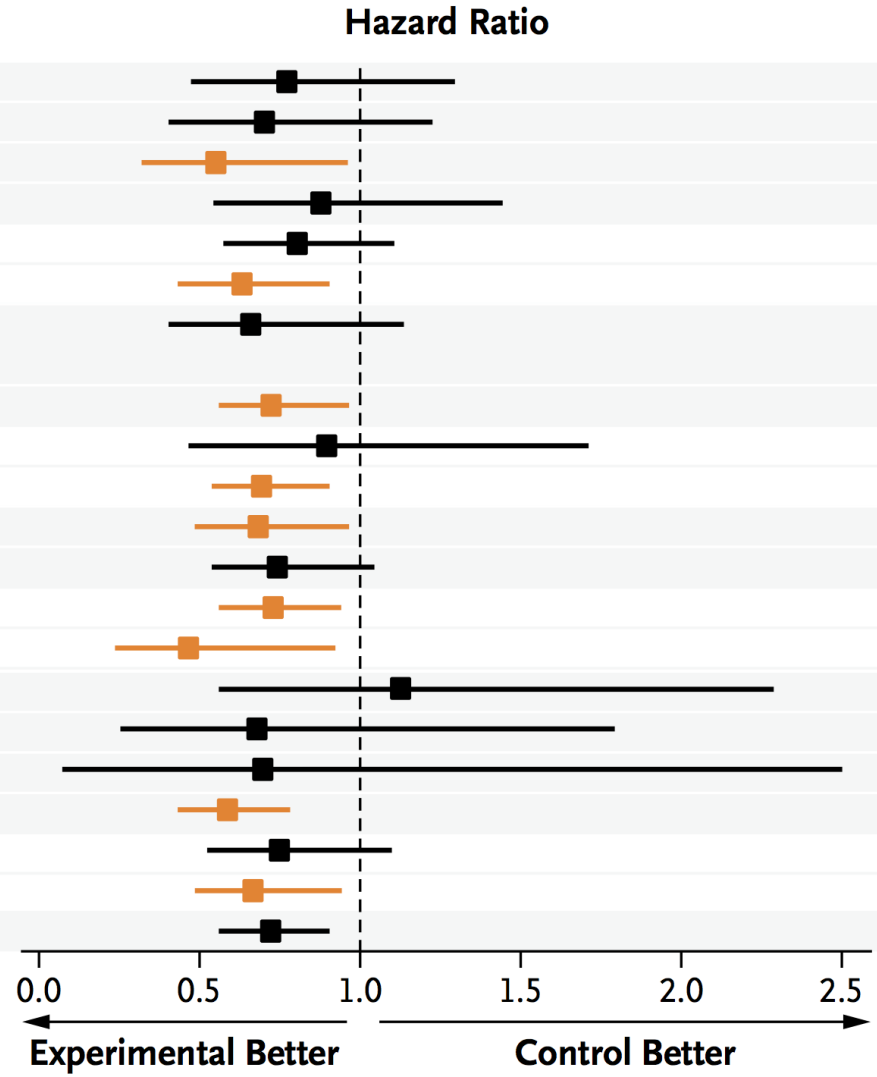


No. at Risk						
TP	111	78	44	23	5	3
TP+bev	115	90	58	32	13	5

Tewari NEJM 2014

GOG-0240: Subgroup Analysis

Subgroup		No. of Patients
Age	≤40 yr	112
	40 to ≤48 yr	111
	48 to ≤56 yr	108
	>56 yr	121
Performance status	0	263
	1	189
Previous platinum radiation therapy	No	115
	Yes	337
Disease status	Advanced	76
	Recurrent or persistent	376
Topotecan treatment	No	229
	Yes	223
Race	Not black	392
	Black	60
Histologic type	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic disease	No	210
	Yes	242
Overall		452



GOG-240: Moore Risk Stratification

- Planned subgroup analysis
- Moore risk criteria established on 429 patients treated on GOG-110, GOG-169, GOG-179 and validated in GOG-149 (all phase III trials)

Factor	Points	
	0	1
Performance Status	0	>0
Pelvic Disease	Absent	Present
African American	No	Yes
Disease Free Interval	≥ 12 mos	<12 mos
Prior Platinum	No	Yes

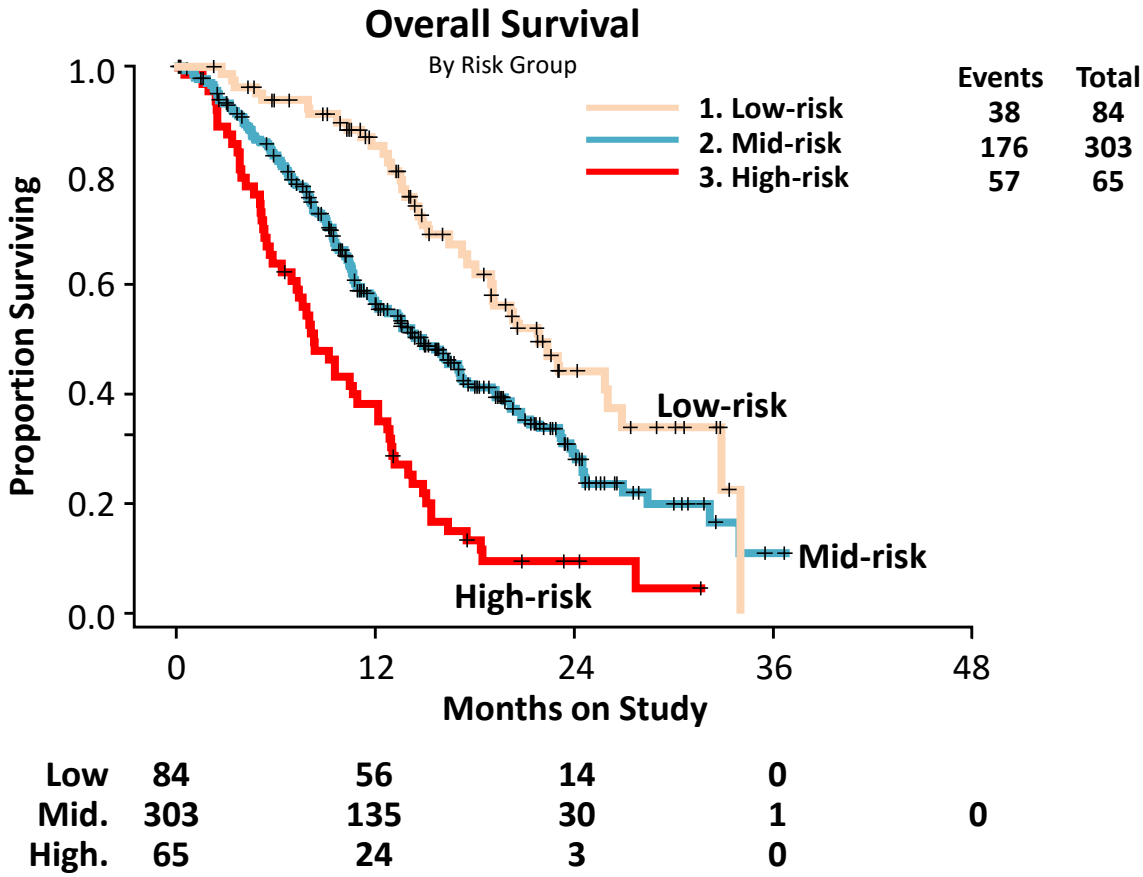
Risk:

- **Low: 0-1**
- **Mid: 2-3**
- **High: 4-5**

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

GOG 240: Validation of The Moore Criteria

Entire Study Population: Arms 1-4

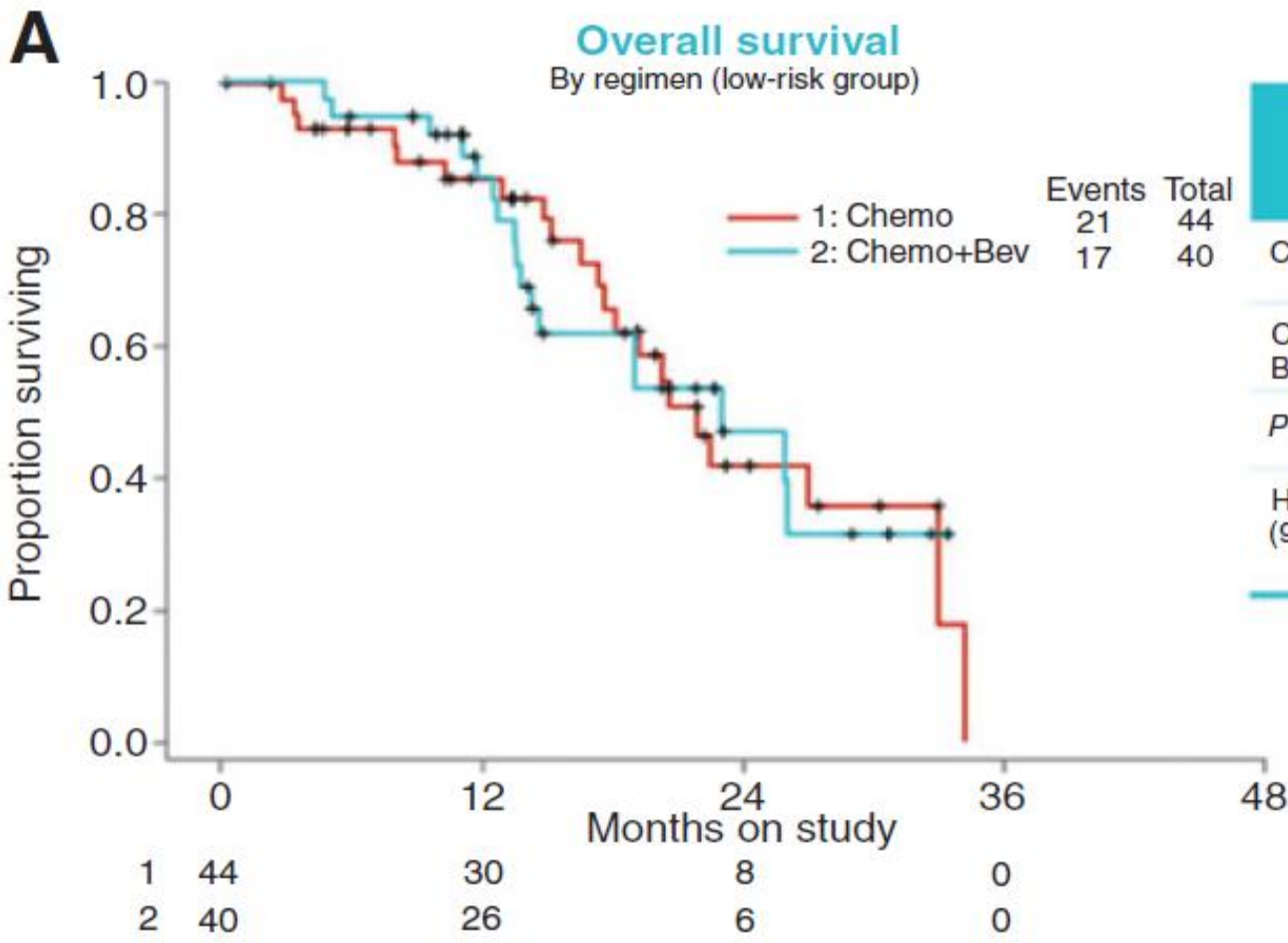


	Median OS (months)	Median PFS (months)	RR (%)
Low-risk	21.8	9.2	57.1
Mid-risk	14.7	6.9	43.2
High-risk	8.2	4.7	18.5
P (likelihood ratio)	<.0001	.0050	<.0001

Tewari KS, et al. Presented at: Society of Gynecologic Oncology 45th Annual Meeting on Women's Cancer; March 22-25, 2014; Tampa, Flordia. Abstract 44-45.

Overall Survival by Regimen: Low Risk

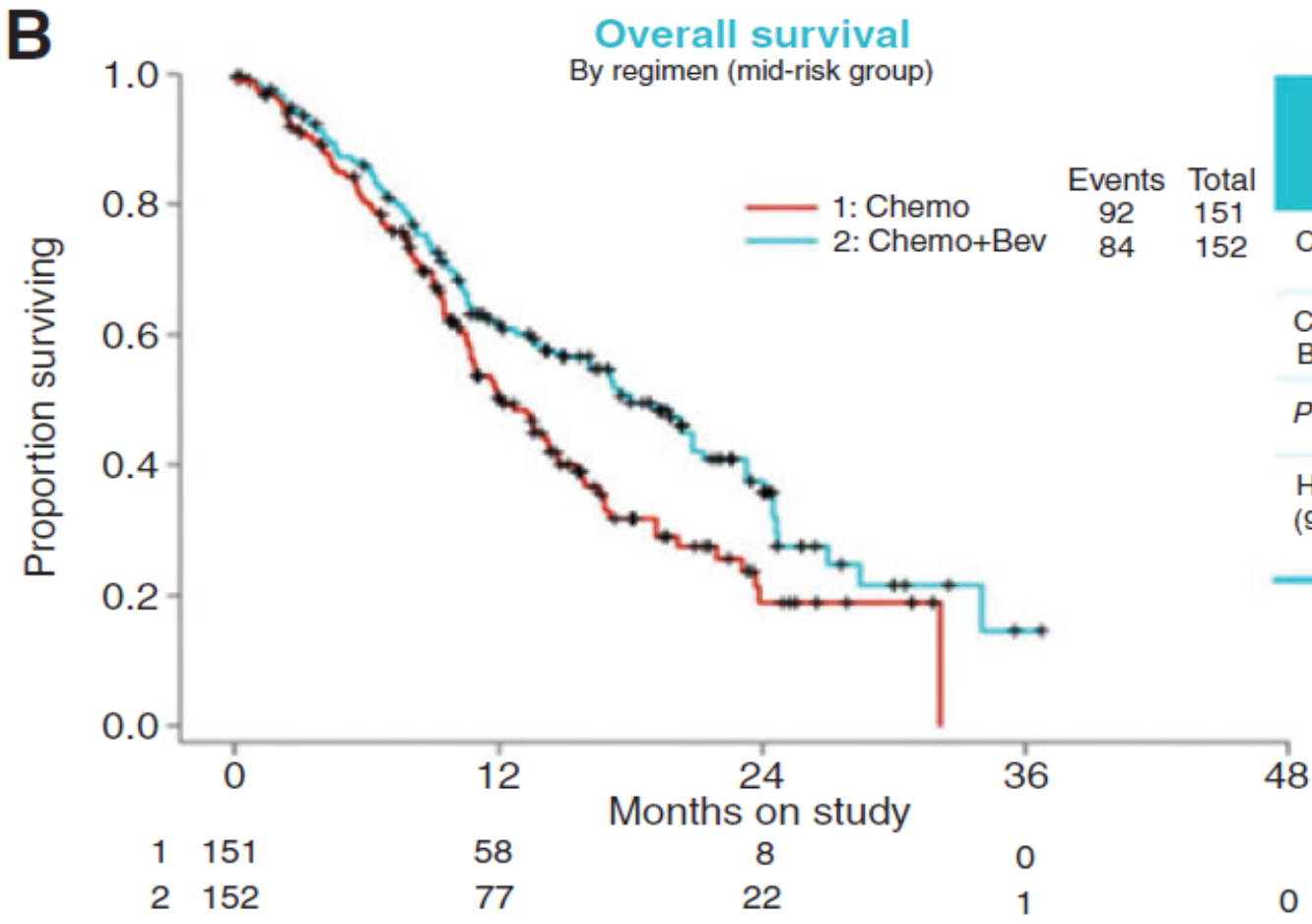
19% of Sample



	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	21.8	8.0	52.0
Chemo + Bev	22.9	10.9	62.5
P	0.9087	0.2903	<0.3435
HR (95% CI)	0.96 (0.51–1.83)	0.85 (0.53–1.37)	1.522 (0.64–3.64)

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Overall Survival by Regimen: Mid Risk



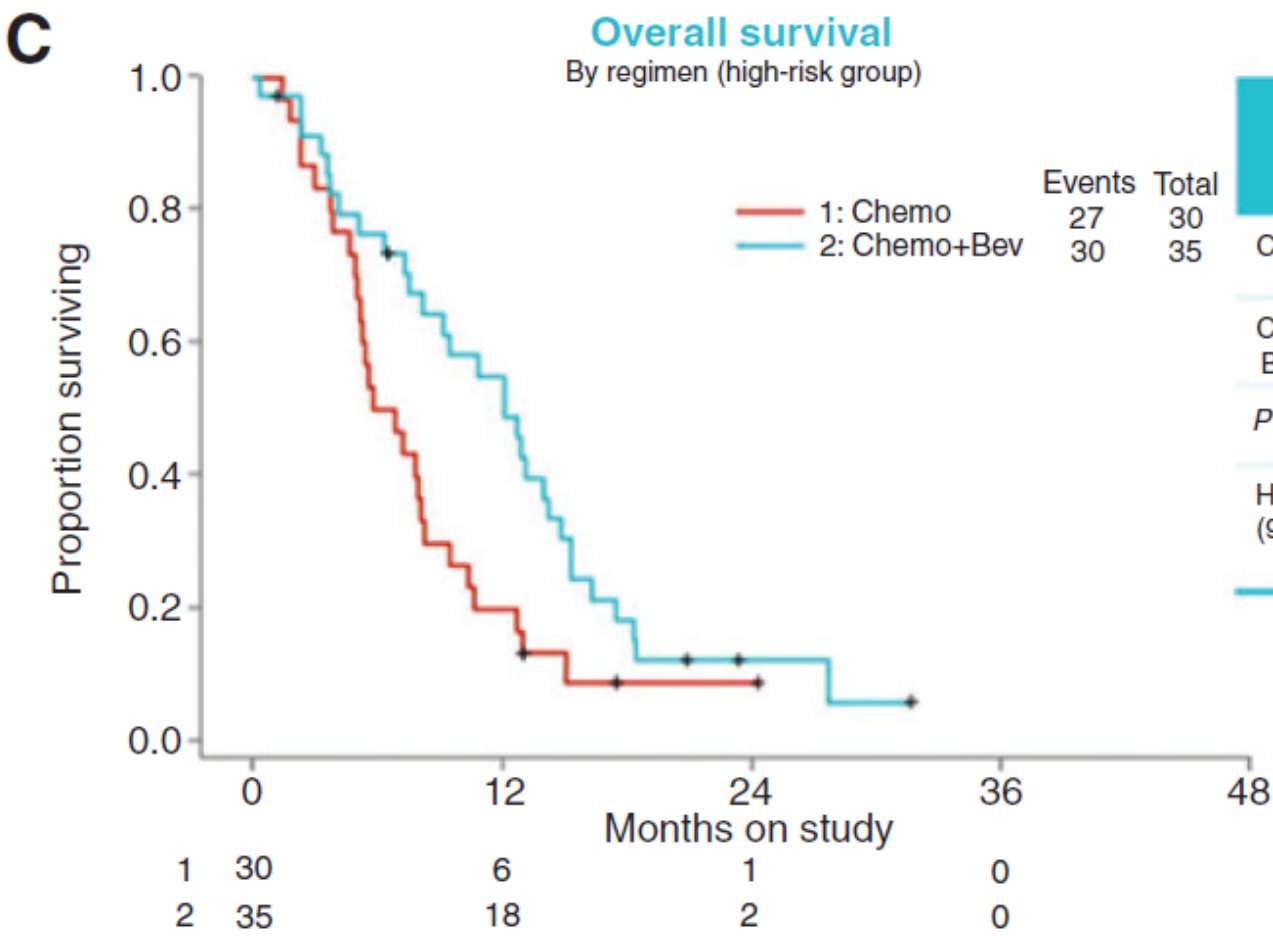
67% of Sample

	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	12.1	5.8	36.0
Chemo + Bev	17.9	7.9	50.7
P	0.0094	0.0047	<0.0087
HR (95% CI)	0.673 (0.51–0.91)	0.694 (0.54–0.89)	1.844 (1.16–2.92)

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Overall Survival by Regimen: High Risk

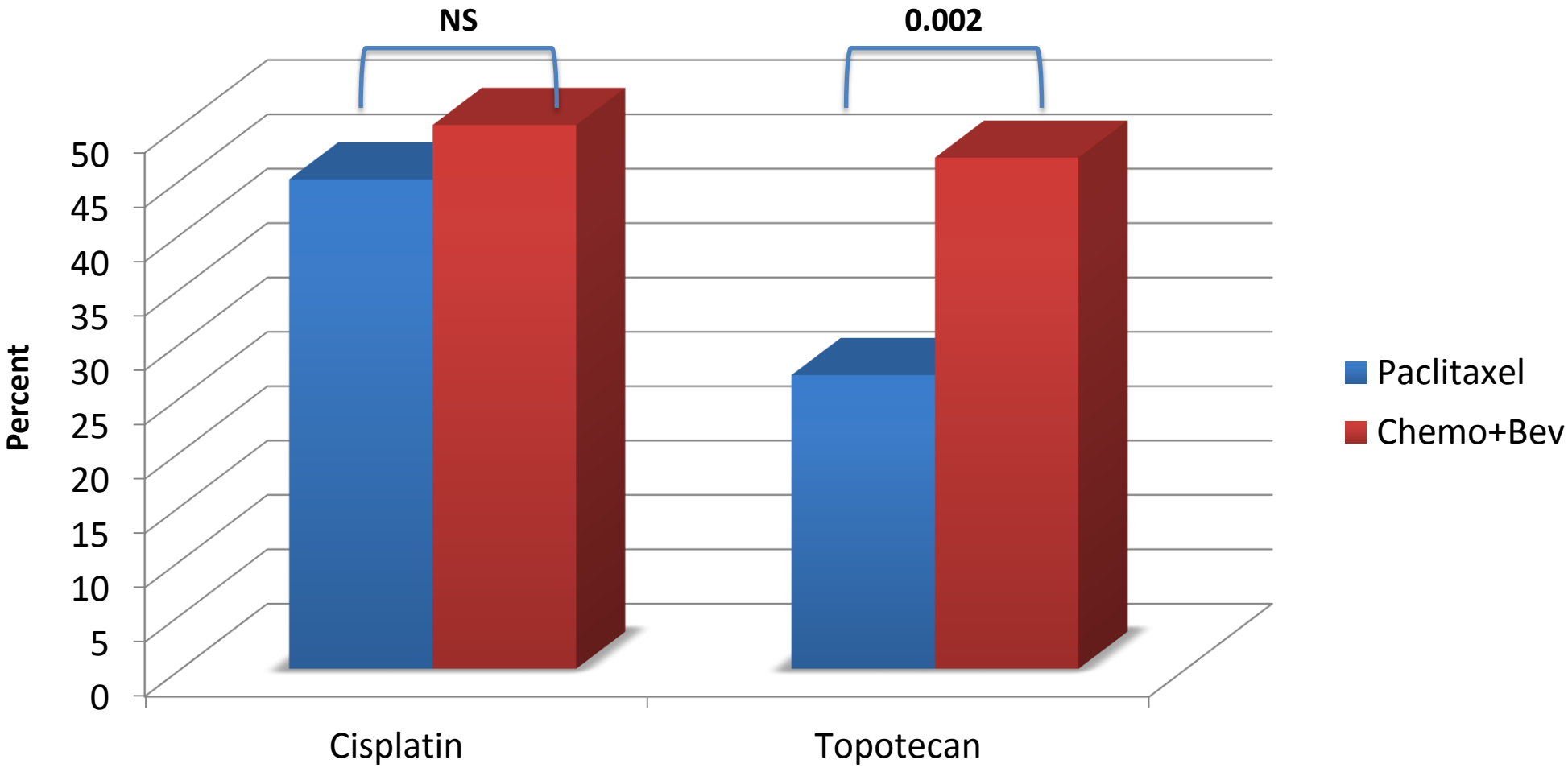
14% of Sample



	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	6.3	3.0	13.0
Chemo + Bev	12.1	6.0	22.9
P	0.0196	0.0272	<0.3190
HR (95% CI)	0.536 (0.32–0.905)	0.506 (0.277–0.926)	1.926 (0.52–7.18)

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Objective Response



GOG/NRG Oncology CTCAE v 3,4

Updated Toxicity Profile

Adverse Event, n (%)	Chemo Alone (n=220)	Chemo + Bev (n=220)
Treatment cycles, median (range)	6 (1-50)	7 (1-40)
Grade 5 AE(s)	3 (1.3)	7 (3.2)
GI events, non-fistula (grade ≥2)	97 (44)	115 (53)
GI fistula (grade ≥2)	1(0.5)	11 (5)
GI perforation (grade ≥2)	0 (0)	5 (2.3)
GU fistula (grade ≥2)	1 (0.5)	8 (3.6)
Hypertension (grade ≥2)	4 (1.8)	55 (25)
Proteinuria (grade ≥3)	0 (0)	5 (2.3)
Pain (grade ≥2)	63 (29)	72 (33)
Neutropenia (grade ≥4)	58 (26)	80 (36)
Febrile neutropenia (grade ≥3)	12 (5.5)	12 (5.5)
Thromboembolism (grade ≥3)	4 (1.8)	18 (8.2)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0.5)	4 (1.8)
GU (grade ≥3)	1 (0.5)	6 (2.7)

All patients developing fistula had previous pelvic RT (IGCS 2014)

bev, bevacizuamb; chemo, chemotherapy; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary.

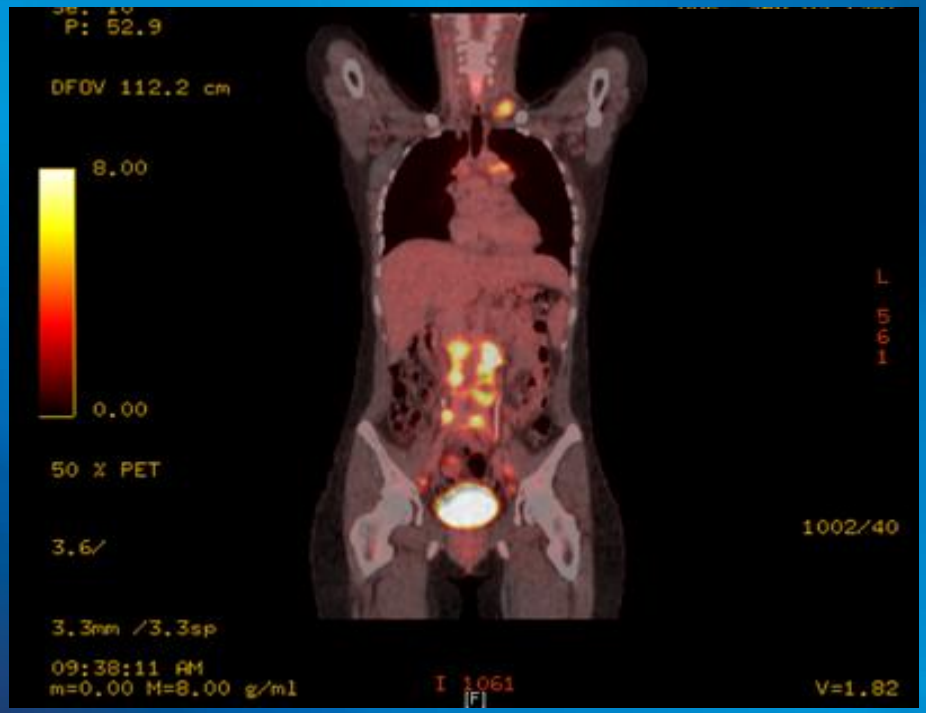
Tewari NEJM 2014

- The patient started on IV cisplatin 50 mg/m^2, paclitaxel 175 mg/m^2 over 3 hours and bevacizumab 15 mg/kg q3w × 6 cycles
- Patient tolerated treatment well – C5 dose delay for 1 week due to hypertension management
- PET/CT repeated after cycle 6

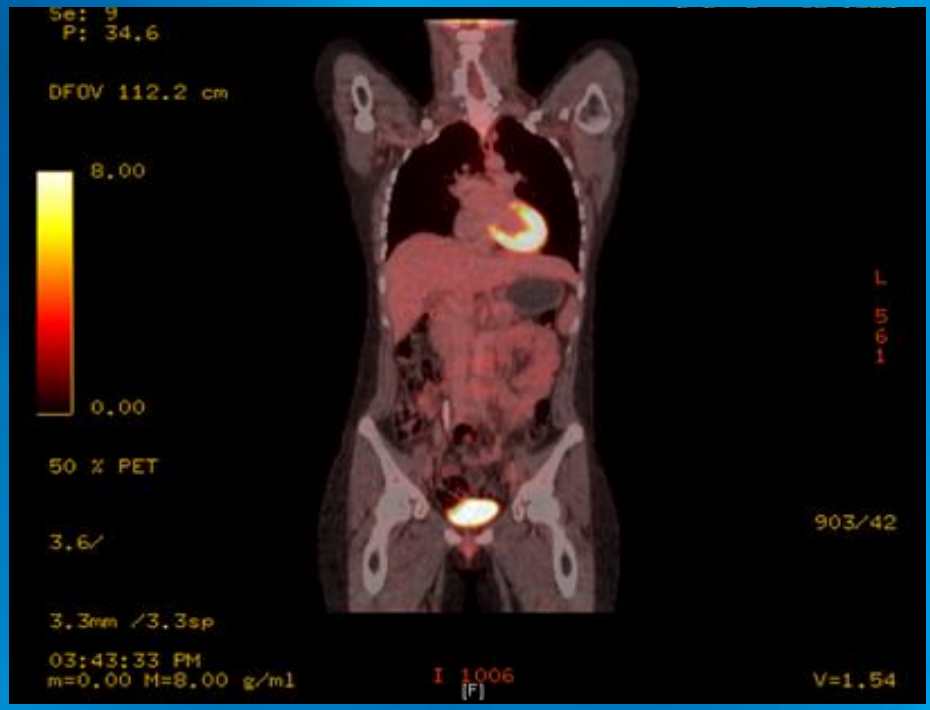
Avastin® (bevacizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2014.

- Patient has responses in lymph nodes and primary tumor after cycle 4
- Patient continued on cisplatin, paclitaxel and bevacizumab
- Repeat PET/CT = NED, treatment discontinued
- On active surveillance (3 month FUV)

Pretreatment PET/CT Scan



PET/CT After Cycle 4



Discussion Questions

- What is the role of maintenance bevacizumab?
  - In GOG-0240, 21/28 CR's discontinued therapy
- Does this patient need radiation now that there has been a CR?
  - Should chemotherapy (+/- bevacizumab) be added to radiation?
  - Should this include brachytherapy or just external beam?
- What is her risk of a fistula?
  - If a fistula occurs on therapy, how is this managed?
- What are the options for recurrence should it occur?

New Directions

- **Immunotherapy and immunomodulators**
  - PD1/PDL-1, CTLA-4, OX-40, 4-1BB, KIR
  - HPV therapeutic vaccines
  - ADXS-HPV
- **PARP**
- **PI3K & MAPK pathway inhibitors**
- **Angiogenesis**
  - Escape (infiltrating macrophages/monocytes, MDSC's, TIL targeting)
  - Hypoxia
  - New targets (Ang1/2, FGFR, TKI's)

Summary

- **Platinum-paclitaxel combination is the standard chemotherapy in patients with adequate PS and renal function**
- **Carboplatin is a reasonable substitute for cisplatin**
- **Bevacizumab added to standard chemotherapy prolongs overall survival, without a significant impact on QoL**
- **More agents = more toxicity (legitimate concerns for fistula in radiated patients)**
- **Next step is to optimize the use of bevacizumab and to integrate new targeted therapies**

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