Update on Targeted Therapy and Immunotherapy for Cervical Cancer

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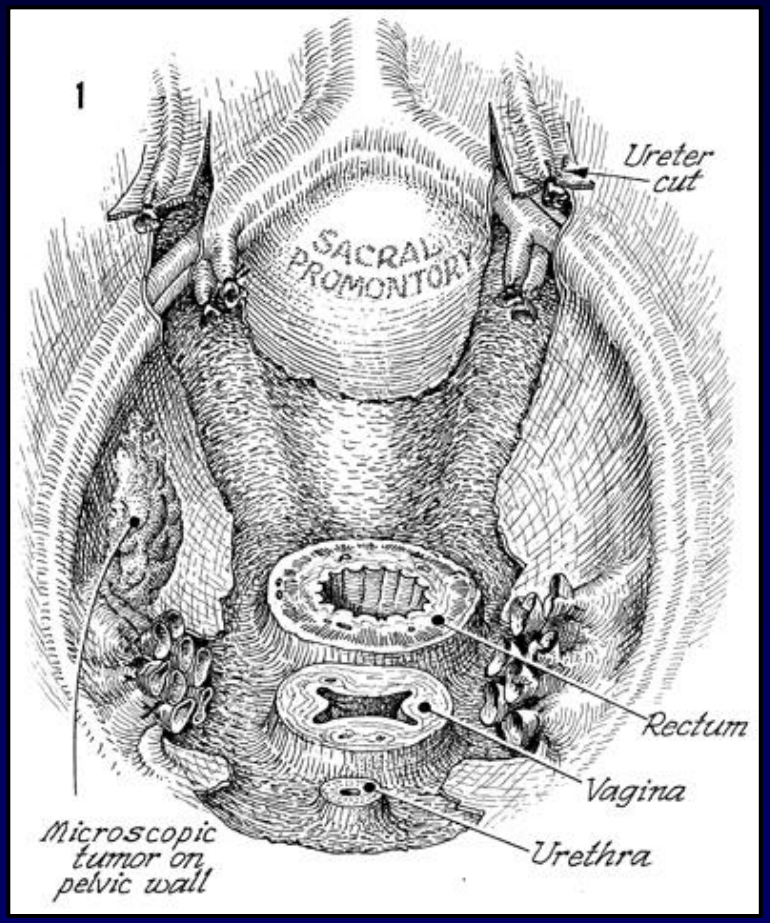
prIME oncology

Alexander Brunschwig

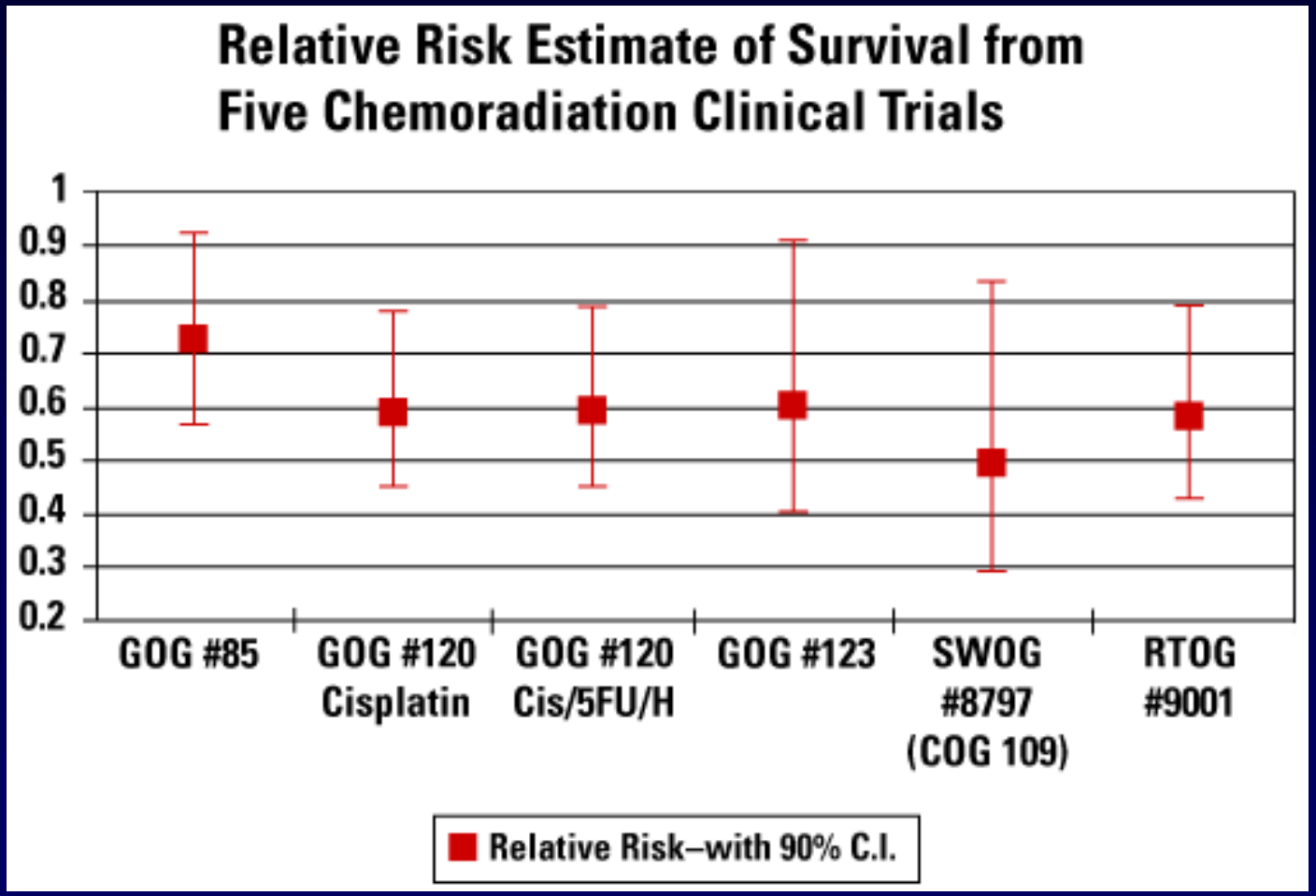
Total Pelvic Exenteration for Isolated Central Recurrences

1901-1969



Brunschwig A. *Cancer.* 1948;1(2):177-183.

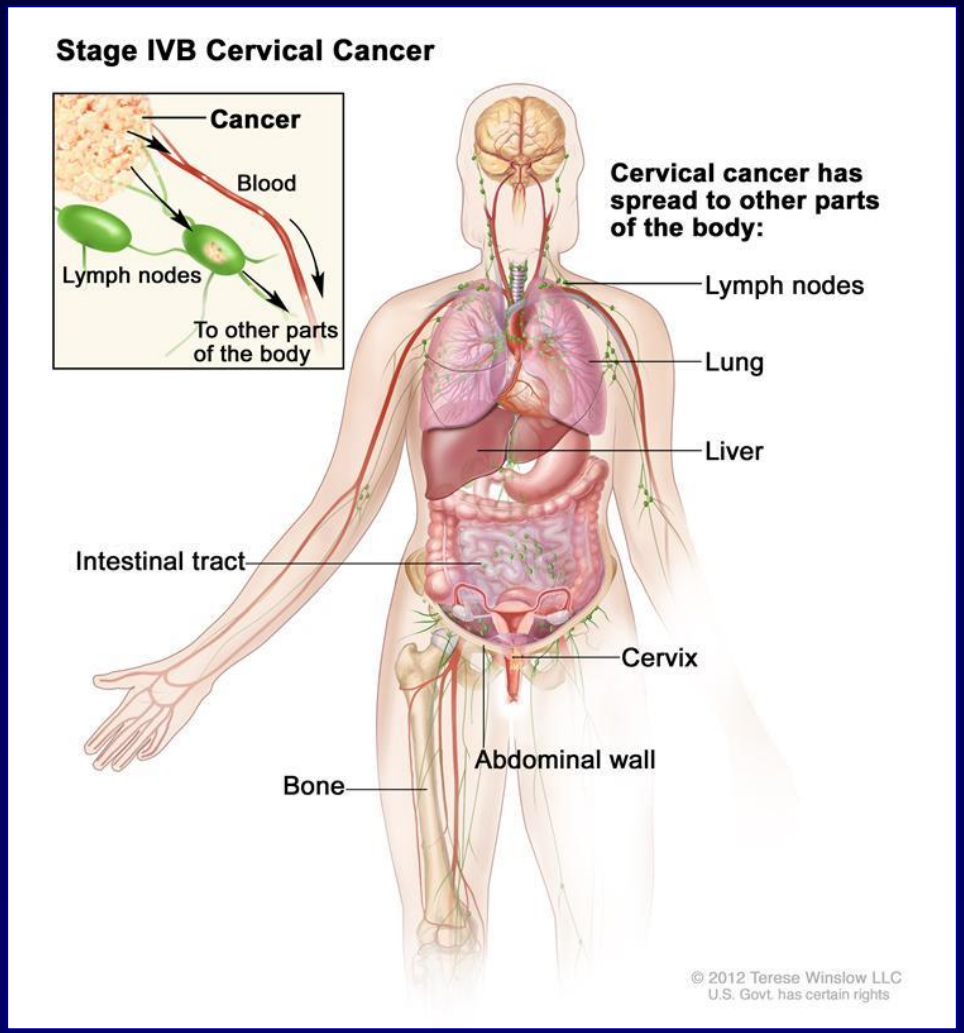
5 Pivotal Trials of Chemoradiation



National Cancer Institute Clinical Announcement 1999: www.cancer.gov/cancertopics/types/cervical

Morris M, et al. *N Engl J Med*. 1999;340(15):1137-1143. Rose PG, et al. *N Engl J Med.* 1999;340(15):1144-1153. Keys HM, et al. *N Engl J Med.* 1999;340(15):1154-1161. Whitney CW, et al. *J Clin Oncol.* 1999;17(5):1339-1348. Peters WA 3rd, et al. *J Clin Oncol.* 2000;18(8):1606-1613.

Recurrent/Persistent and Metastatic Disease: A HIGH UNMET CLINICAL NEED!



Recurrent and Metastatic Cervical Cancer

- Cisplatin (Cis) 50 mg/m2 plus paclitaxel (Pac) 135 mg/m2 standard therapy
  - Median overall survival (OS) ≤12 months
- Majority of patients with recurrent cervical cancer treated with cisplatin-based chemoradiation for locally advanced disease (1999 onwards)
  - Concern that acquired drug resistance may make platinum-based therapies less effective for recurrent cervical cancer
- Gynecologic Oncology Group (GOG) 204 (2009)*
  - Phase III randomized trial of 4 platinum-based chemotherapy doublets
  - Closed for futility
  - Cisplatin plus paclitaxel remained standard
  - New therapeutic options needed
  - Non-platinum chemotherapy doublets?
  - Anti-angiogenesis therapy?

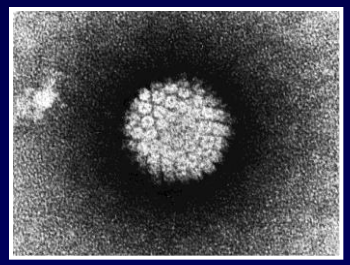
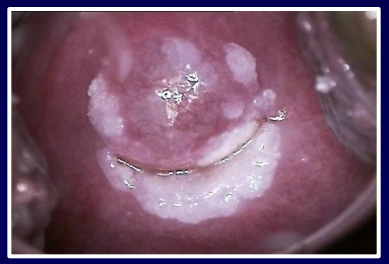
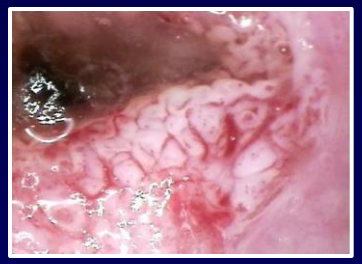
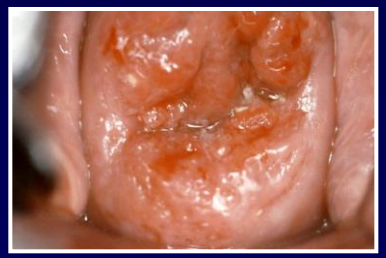
Tewari KS, et al. *Curr Oncol Rep.* 2005;7(6):419-434. Monk BJ, et al. *J Clin Oncol.* 2007;25(20):2952-2965. Tewari KS, et al. *Onkologie.* 2008;32(10):552-554. *Monk BJ, et al. *J Clin Oncol.* 2009;27(28):4649-4655. Tewari KS, et al. *Semin Oncol.* 2009;36(2):170-180. Tewari KS, et al. *Clin Adv Hematol Oncol.* 2010;8(2):108-115. Tewari KS. *Am J Hematol Oncol.* 2010;9:31-34. Tewari KS. *Clin Ovarian Cancer.* 2011;4:90-93.

HPV Infection + Angiogenesis = Progressive Cervical Neoplasia

Transient infection → Persistent infection

Normal → Precancerous, potential to regress or persist to severe disease → Invasive

HPV infection	CIN 1,2	CIN 2,3[1]	Cervical cancer[2]
		7-10 years[1]	≥10 years[2]

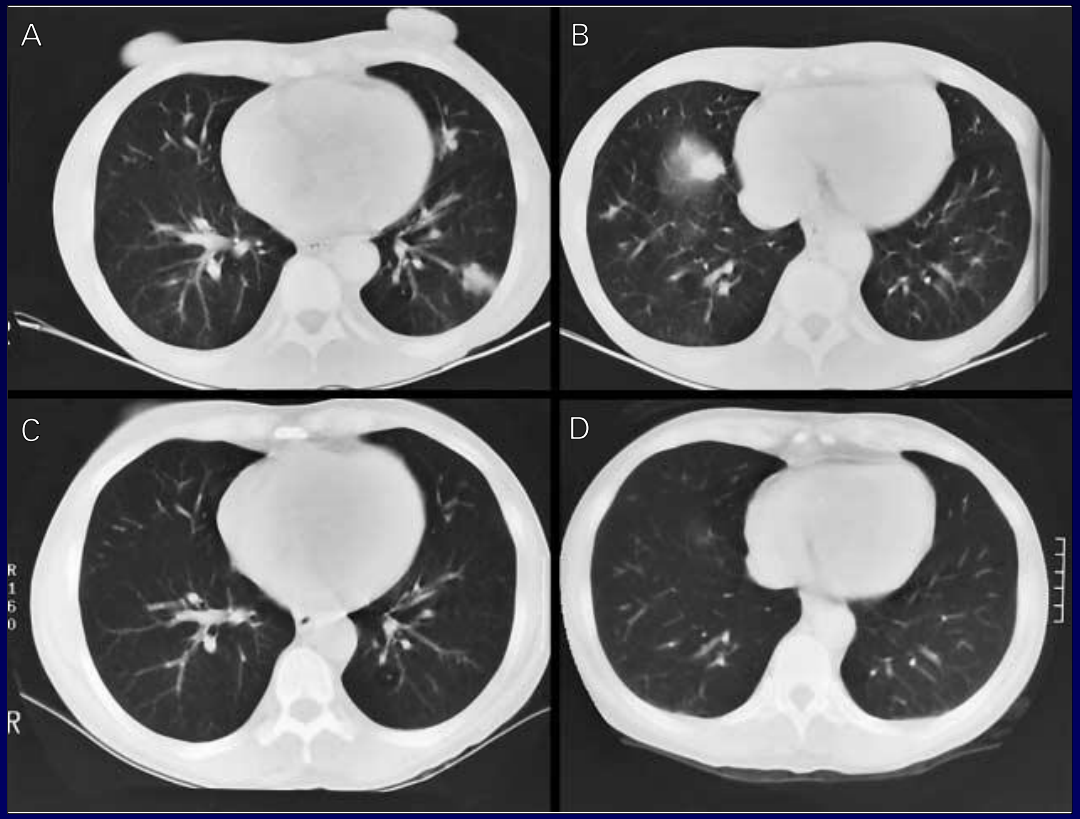





Colposcopy demonstrates abnormal vasculature and angiogenesis dependent progression of cervical neoplasia

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus

1. Schiffman M, et al. *J Int Cancer Natl Monogr*. 2003;31:14-19. 2. Ostör AG. *Int J Gynecol Pathol.* 1993;12(2):186-192.

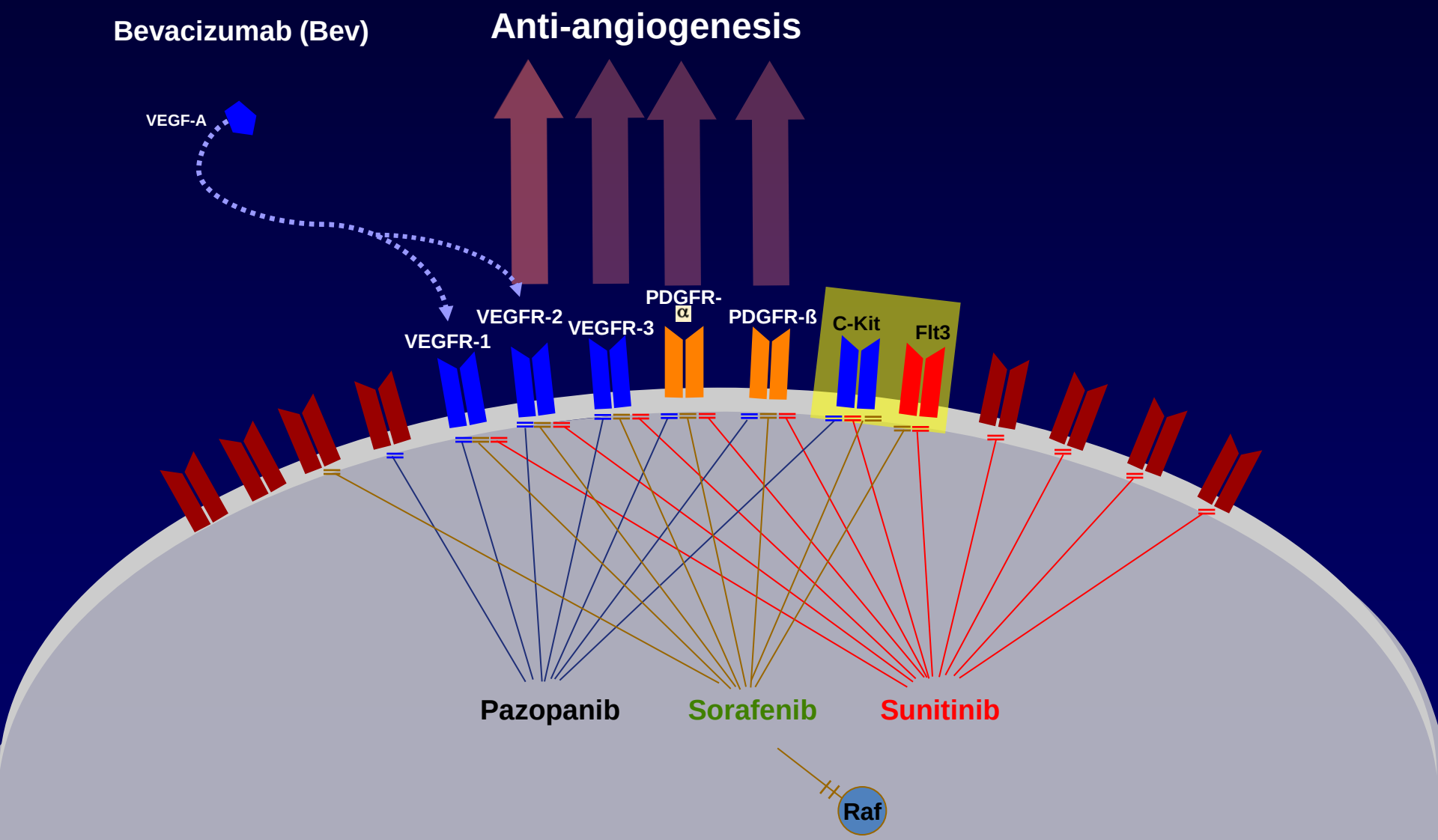
Complete Remission of Metastatic Cervical Cancer With the Angiogenesis Inhibitor TNP-470



- ✓ **Potent fungal metabolite first isolated from Aspergillus fumigatus with anti-angiogenesis properties**

Kudelka AP, et al. *N Engl J Med*. 1998;338(14):991-992.

Mechanism of Action of Early Anti-Vascular Agents

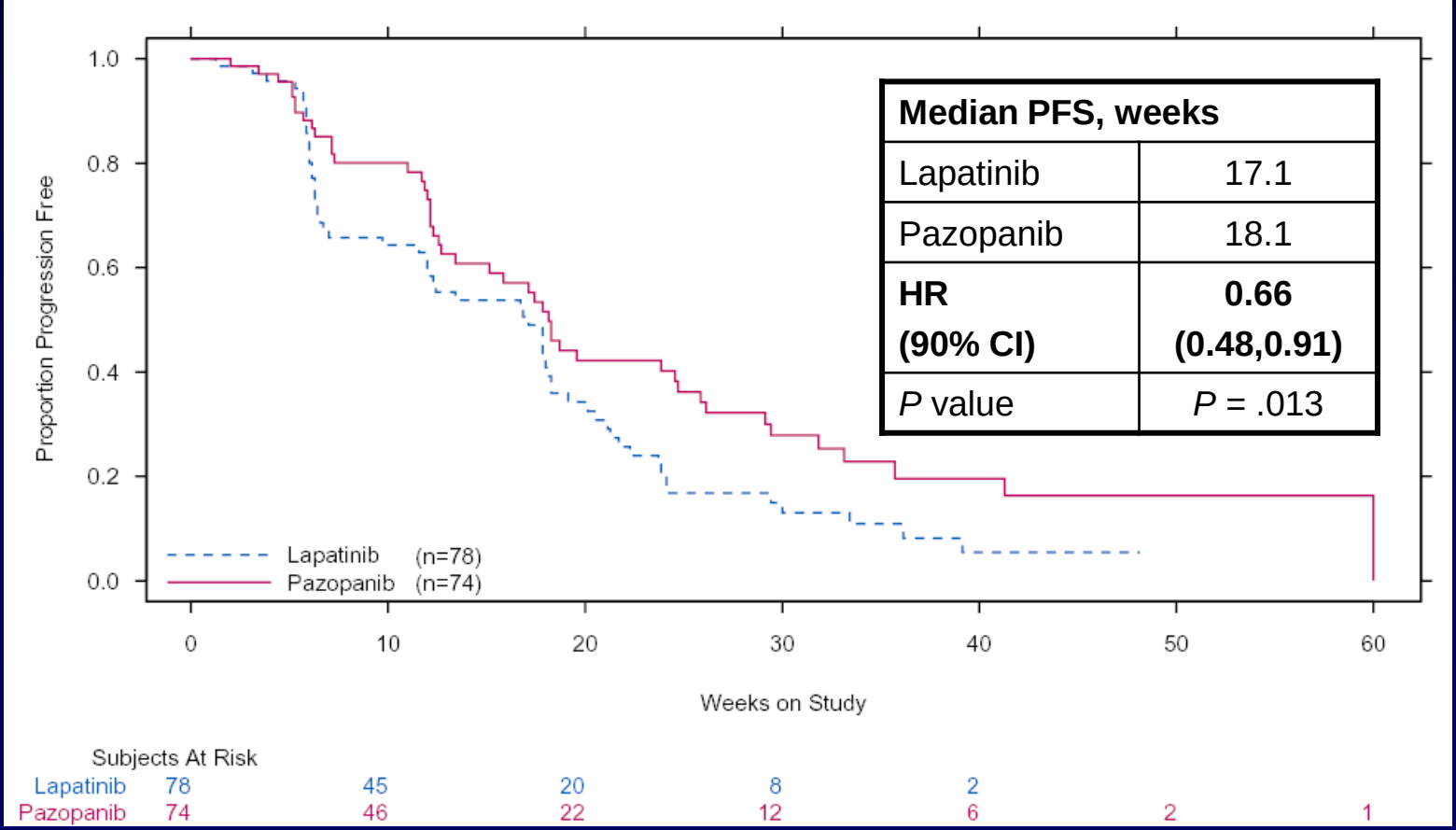


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II, Open-Label Study of Pazopanib or Lapatinib Monotherapy Compared With Pazopanib Plus Lapatinib Combination Therapy in Patients With Advanced and Recurrent Cervical Cancer

Anti-VEGF Out Performs Anti- EGF

Progression-free survival (PFS): ITT



Median PFS, weeks	
Lapatinib	17.1
Pazopanib	18.1
HR (90% CI)	**0.66 (0.48,0.91)**
P value	*P* = .013

**The CI are 90% (alpha = 10%) naïve CIs. *Wald normal approximation is used to calculate the 1-sided *P* value. ***Stratified log-rank *P* value and hazard ratio (Pike) adjusted only for one of the stratification factors – prior chemotherapy.

VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; ITT, intent-to-treat

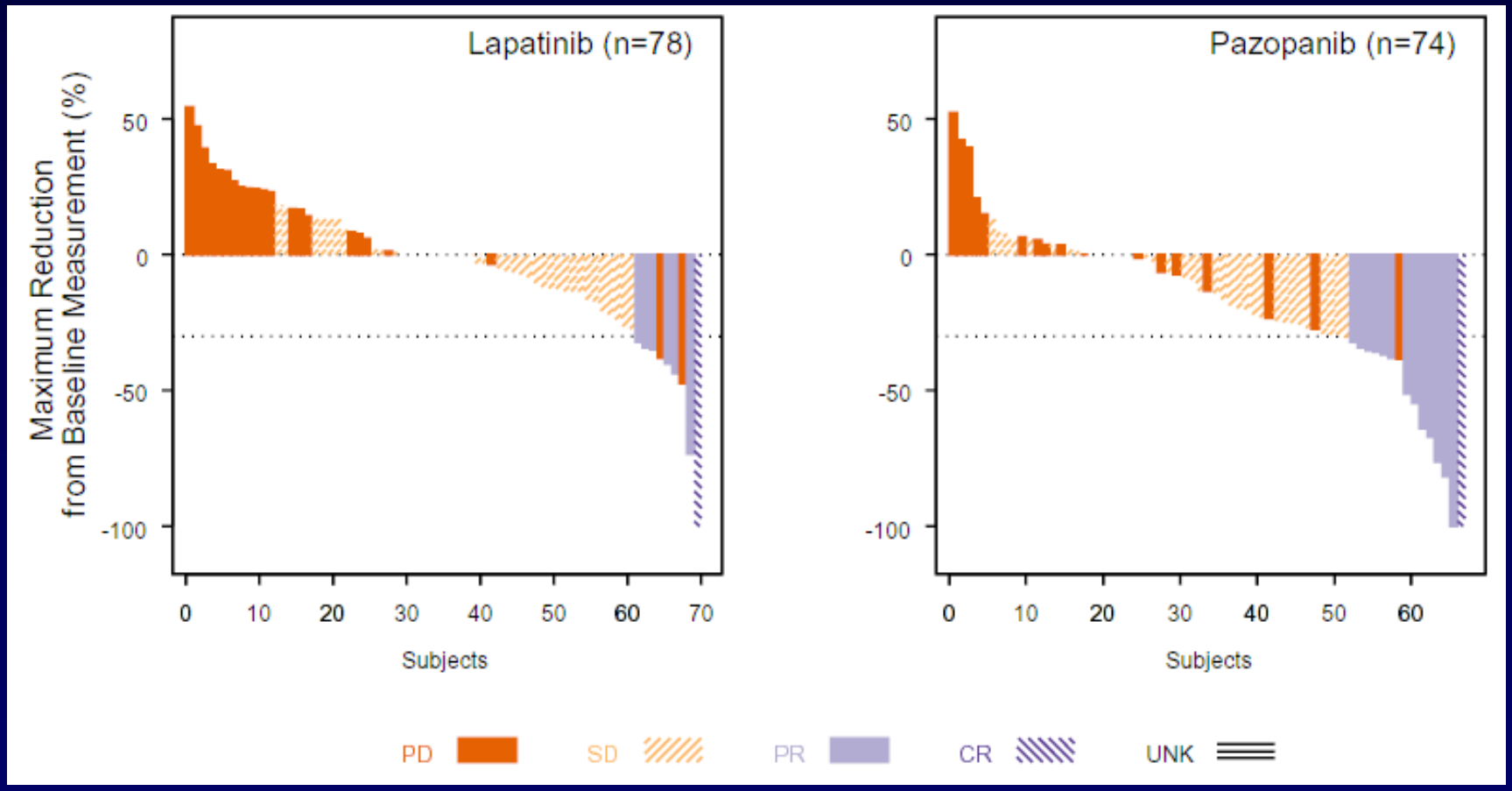
Monk BJ, et al *J Clin Oncol*. 2010;28(22):3562-3569.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II, Open-Label Study of Pazopanib or Lapatinib Monotherapy Compared With Pazopanib Plus Lapatinib Combination Therapy in Patients With Advanced and Recurrent Cervical Cancer

Anti-VEGF Out Performs Anti- EGF

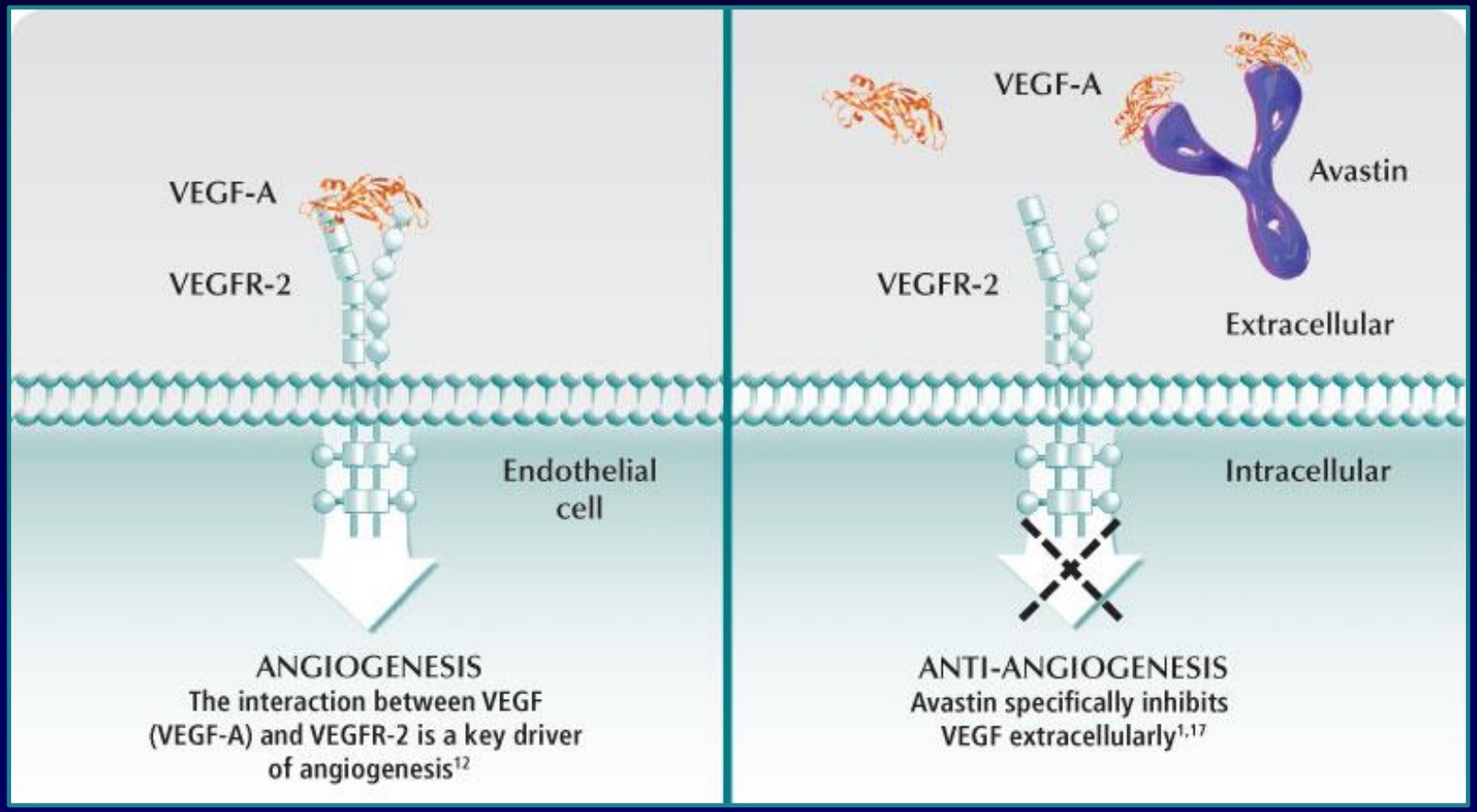
Maximum decrease in target lesion diameter: Lapatinib vs Pazopanib



Monk BJ, et al *J Clin Oncol*. 2010;28(22):3562-3569.

GOG 227C

Phase II Bevacizumab, Recurrent Cervical Cancer



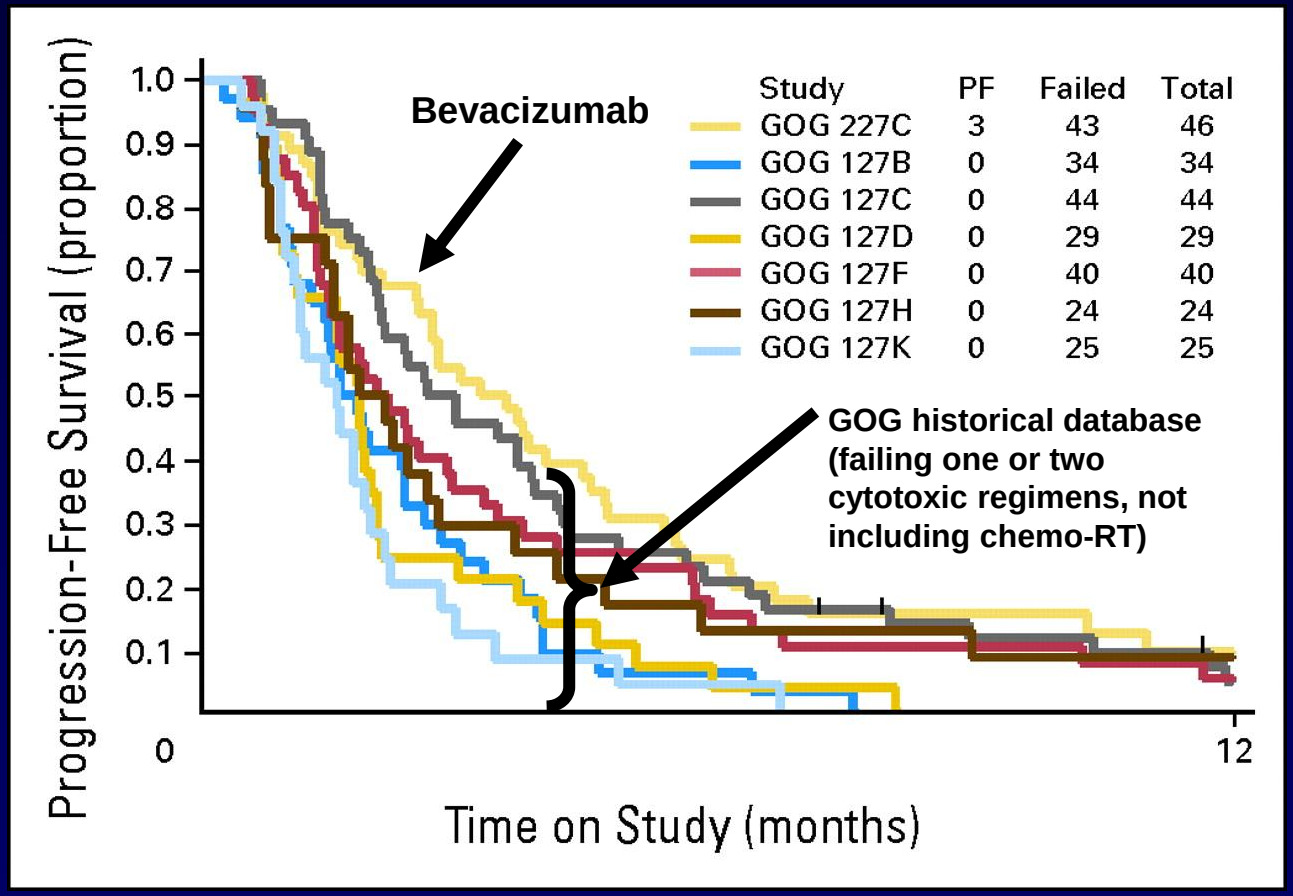
Monk BJ, et al. *J Clin Oncol.* 2009;27(7):1069-1074.

GOG 227C

Phase II Bevacizumab, Recurrent Cervical Cancer

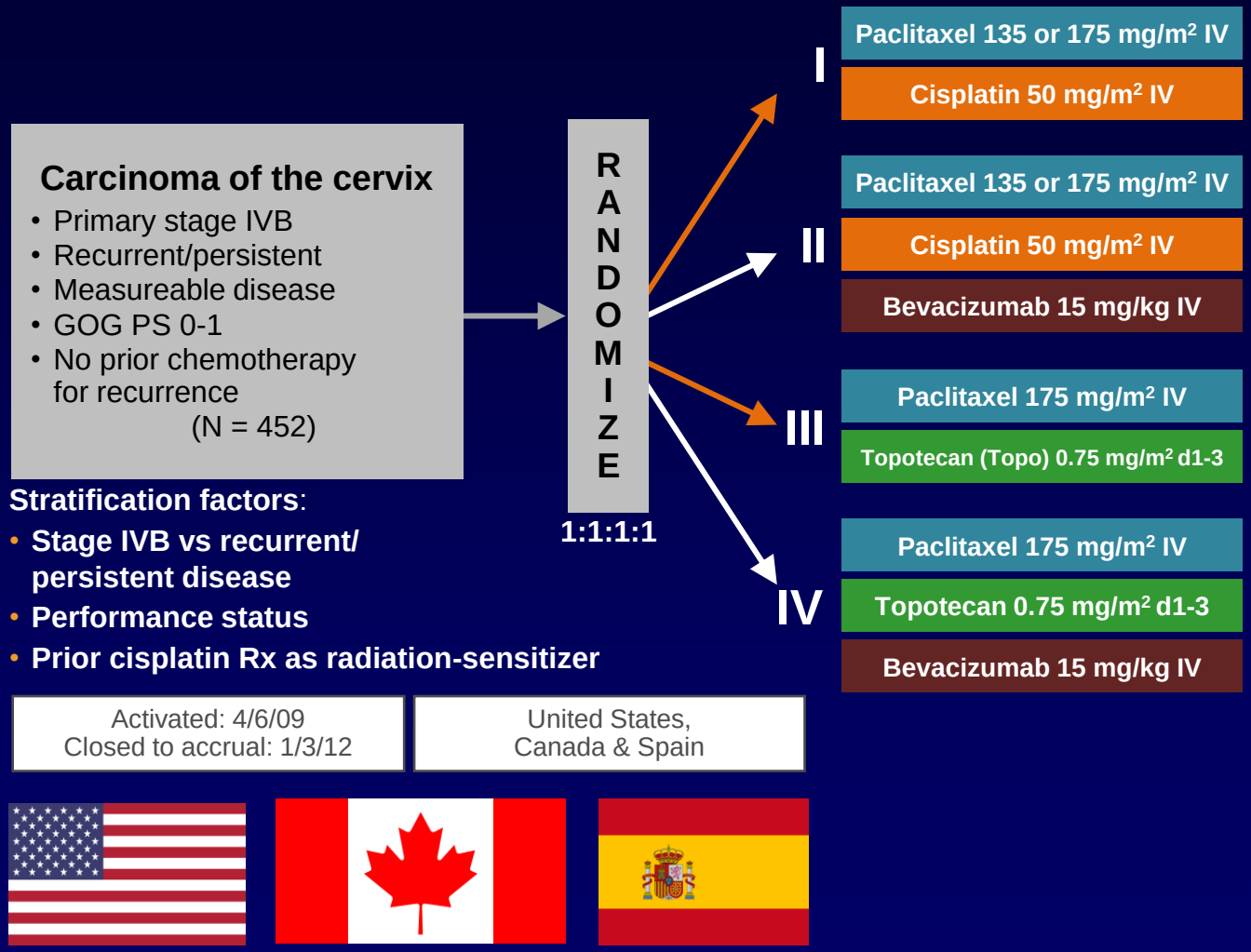
PFS of Bev versus GOG historical database (failing one or two cytotoxic regimens, not including chemo-radio-therapy (RT)

PFS by treatment group



Monk BJ, et al. *J Clin Oncol.* 2009;27(7):1069-1074.

GOG 240: Schema



CR, complete response; PD, progressive disease; PS, performance status; q21d, every 21 days; Rx, treatment

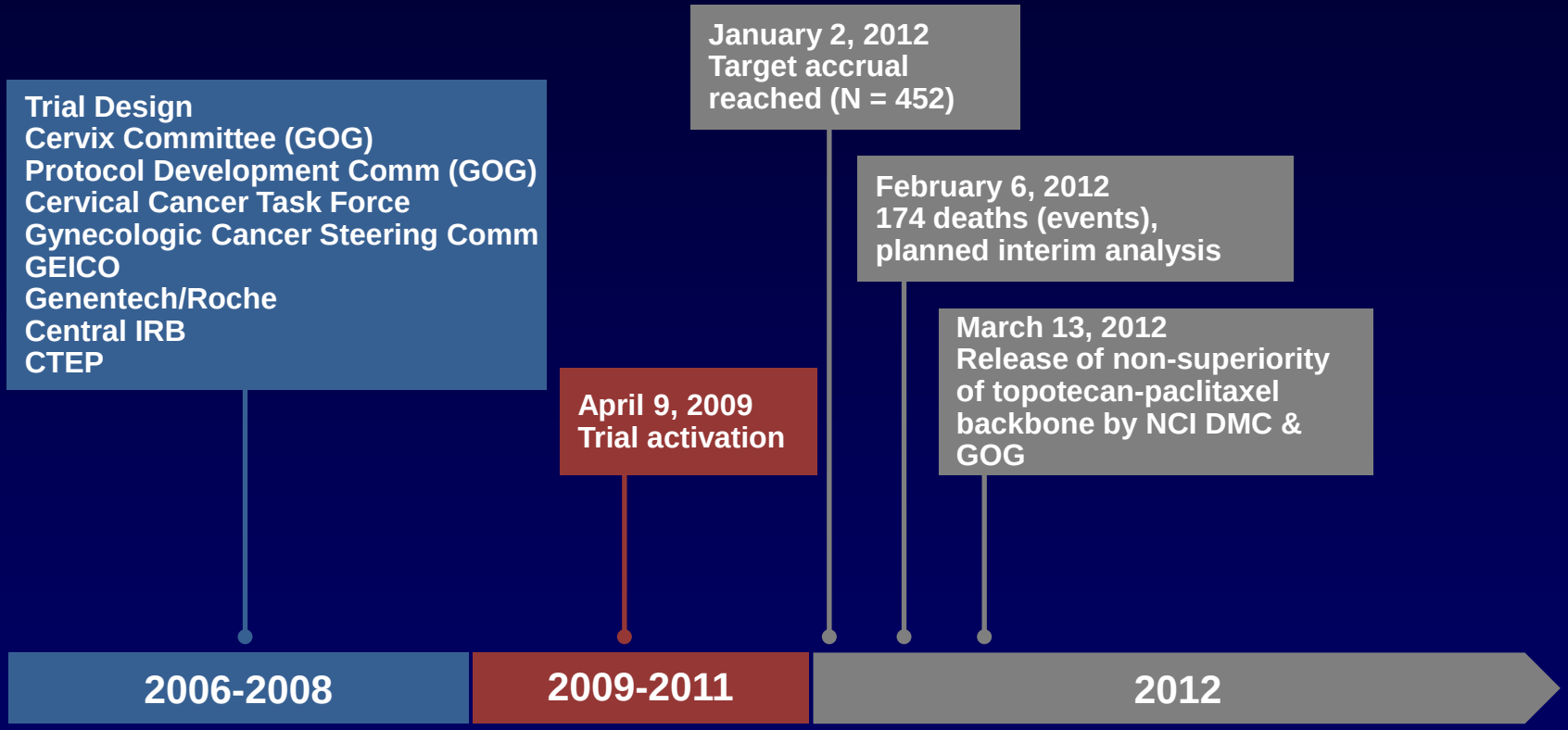
National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

GOG 240: Statistical Considerations

- Phase III open-label study
  - 2 x 2 factorial design with 2 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 overall survival (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%
  - 2.5% alpha for each of the 2 primary hypothesis tests
  - Goal to increase median OS from 12 months to 16 months
- Pre-planned interim analysis after 173 events to determine futility or superiority of either experimental factor
- 2 sequential 2-stage toxicity analyses to monitor for unacceptable toxicity in the experimental arms

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

GOG 240: Study Timeline, Part 1



Comm, Committee; CTEP, Cancer Therapy Evaluation Program; IRB, institutional review board; GEICO, Spanish Ovarian Cancer Research Group

GOG 240.1

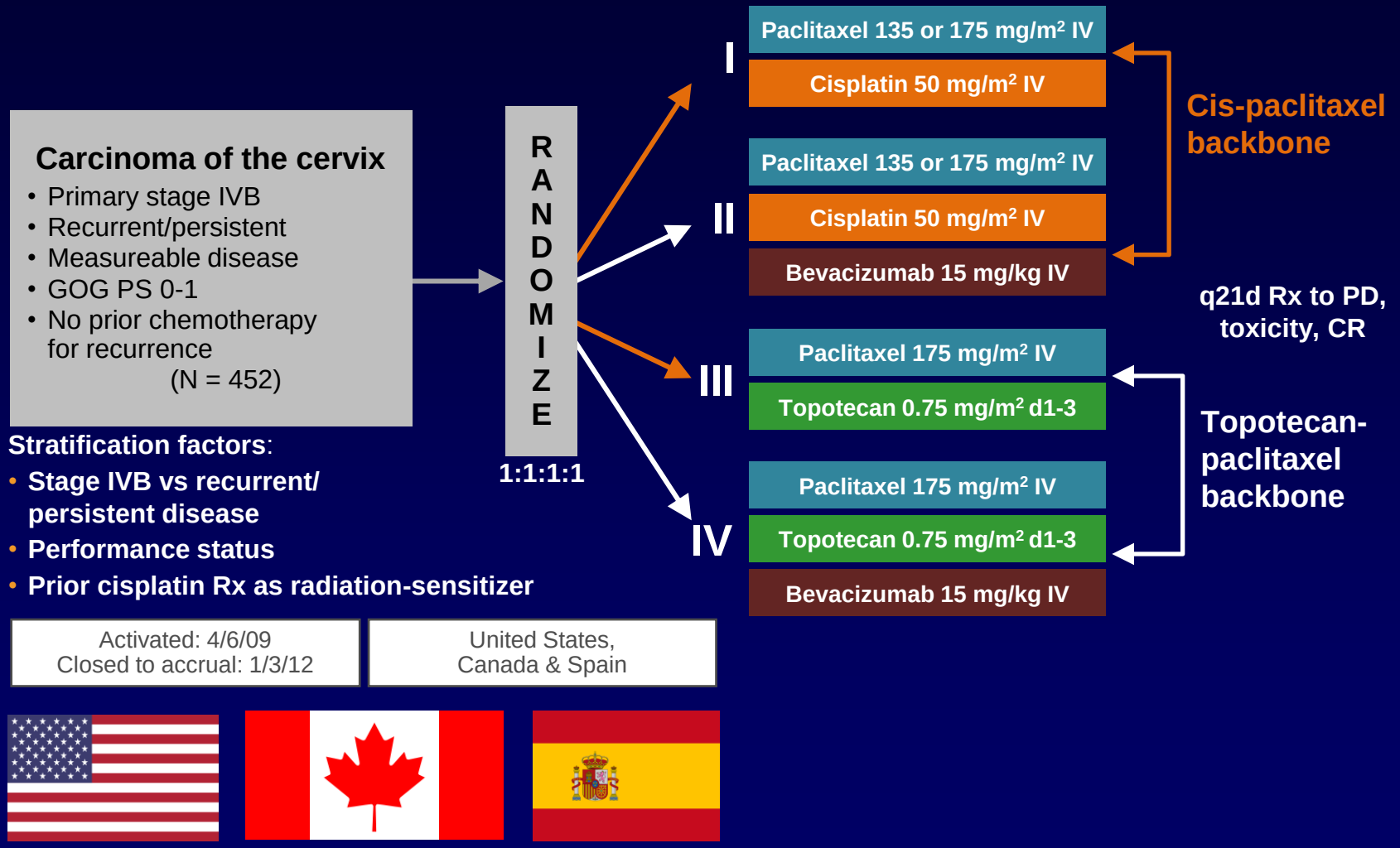
Phase III Randomized Clinical Trial of Cisplatin Plus Paclitaxel vs the Non-Platinum Chemotherapy Doublet of Topotecan Plus Paclitaxel in Women With Recurrent, Persistent, or Metastatic Cervical Carcinoma: A Gynecologic Oncology Group Study

KS Tewari, M Sill, HJ Long III, L Ramondetta, L Landrum, A Oaknin, T Reid, M Leitao, H Michael, BJ Monk

Presented at: The Society of Gynecologic Oncology's (SGO) 2013 Annual Meeting on Women's Cancer
Abstract 1

SGO Presidential Award for Most Outstanding Scientific Abstract
Hugh Barber Lectureship Designation

GOG 240.1: Schema



National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

GOG 240.1: Results
Demographics & Treatment Allocation

	Cis + Pac backbone	Topo + Pac backbone	*P* value
Median age, years	46 (20-85)	48 (22-82)	NS
Squamous	71%	67%	0.308
adenocarcinoma, unspecified	20%	21%	
White	78%	77%	0.800
African American	13%	13%	
Asian	5%	4%	
Pacific Islander	0.4%	0.00	
Recurrent	75%	69%	0.298
Persistent	9%	14%	
Advanced	16%	17%	
PS 0	57%	59%	0.703
PS 1	43%	41%	
Prior platinum	76%	74%	0.666
TOTAL	229	223	NS

Tewari KS, et al. Presented at: The Society of Gynecologic Oncology's 2013 Annual Meeting on Women's Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

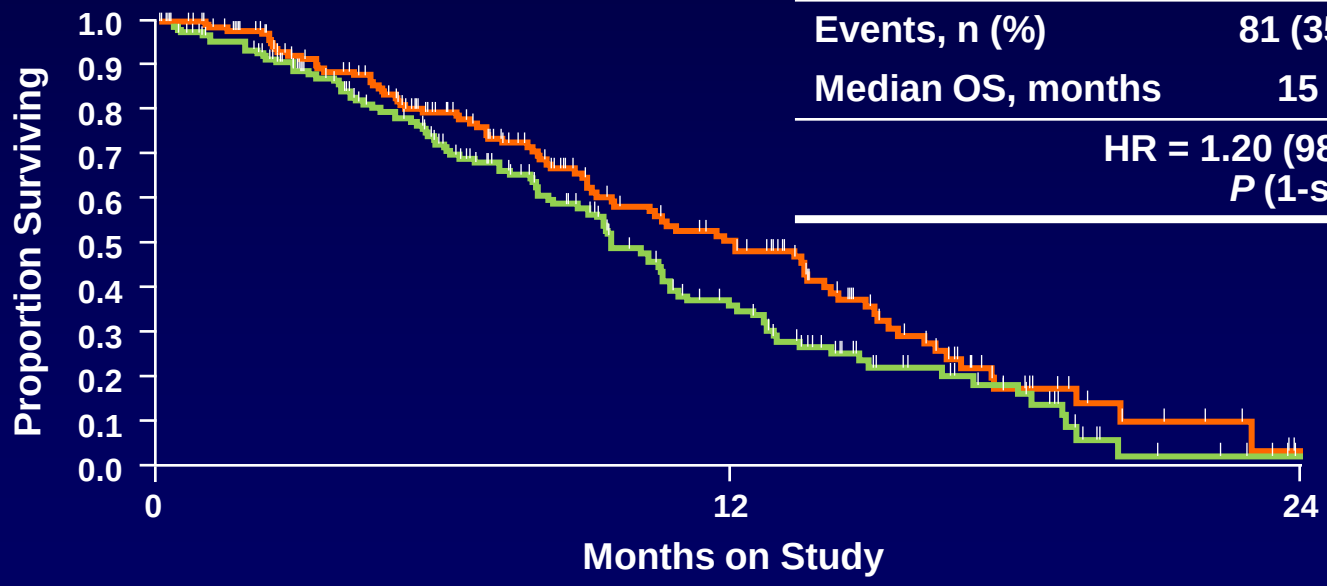
GOG 240.1: Results
Planned Interim Analysis

- February 2012
  - 174 deaths
- NCI DSMB convened
  - Recommended release of topotecan plus paclitaxel data
  - ‘Dear Investigator’ and ‘Dear Patient’ letters drafted

Tewari KS, et al. Presented at: The Society of Gynecologic Oncology’s 2013 Annual Meeting on Women’s Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

GOG 240.1: Interim Analysis SGO 2013
Overall Survival: Cis-Pac Backbone vs Topo-Pac Backbone

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

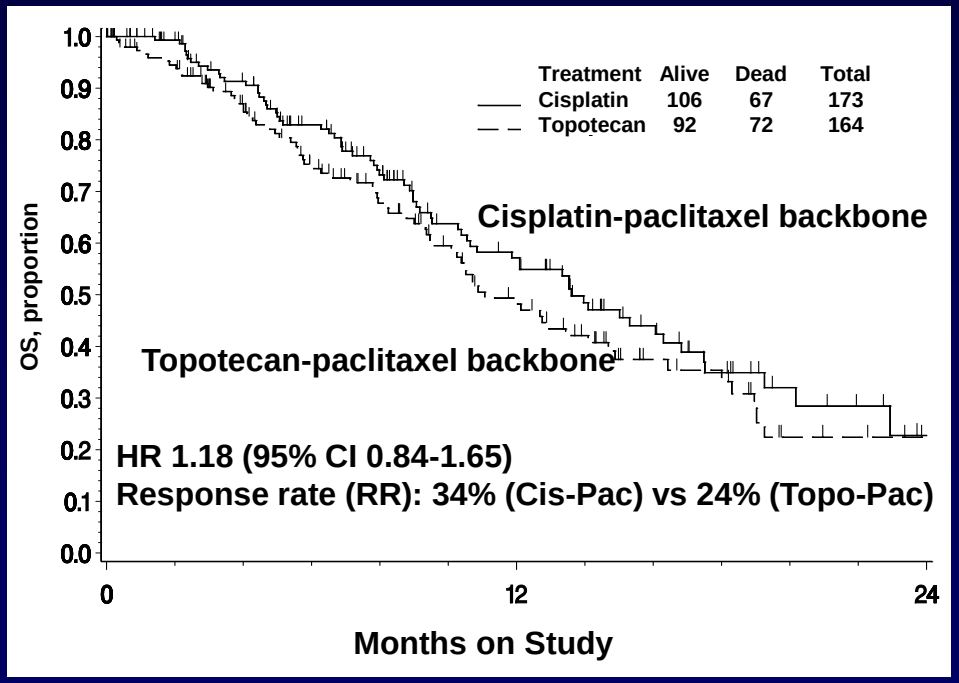


	Cis + Pac (n = 229)	Topo + Pac (n = 223)
Events, n (%)	81 (35)	93 (42)
Median OS, months	15	12.5

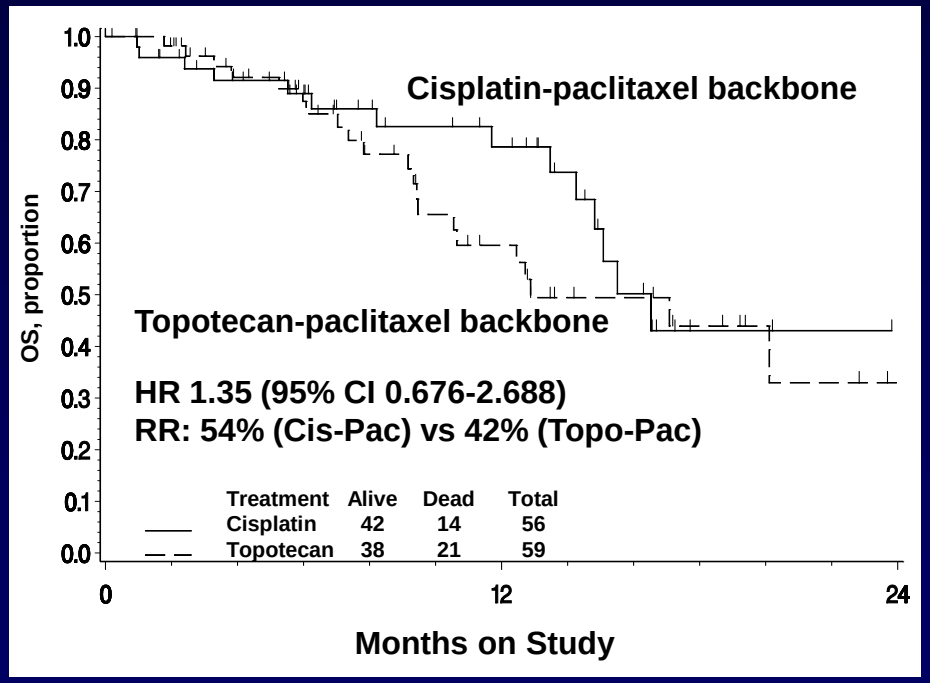
HR = 1.20 (98.74% CI, 0.82-1.76)
P (1-sided) = .880

Tewari KS, et al. Presented at: The Society of Gynecologic Oncology's 2013 Annual Meeting on Women's Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

GOG 240.1: Overall Survival
Prior Platinum Exposure



Prior Cisplatin



No Prior Cisplatin

Tewari KS, et al. Presented at: The Society of Gynecologic Oncology's 2013 Annual Meeting on Women's Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

GOG 240.1: Toxicity

Cis-Pac Backbone vs Topo-Pac Backbone

		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	**Cis-Pac**	45	27	70	60	10	0
	Topo-Pac	30	28	42	71	33	0
Nausea	**Cis-Pac**	82	78	36	16	0	0
	Topo-Pac	103	71	26	4	0	0
Vomiting	**Cis-Pac**	145	29	28	10	0	0
	Topo-Pac	161	27	11	5	0	0
Metabolic	**Cis-Pac**	115	42	28	26	1	0
	Topo-Pac	130	35	26	11	2	0
Neurosensory	**Cis-Pac**	96	65	35	16	0	0
	Topo-Pac	87	82	30	5	0	0
Allergy	**Cis-Pac**	172	16	17	7	0	0
	Topo-Pac	193	7	1	3	0	0

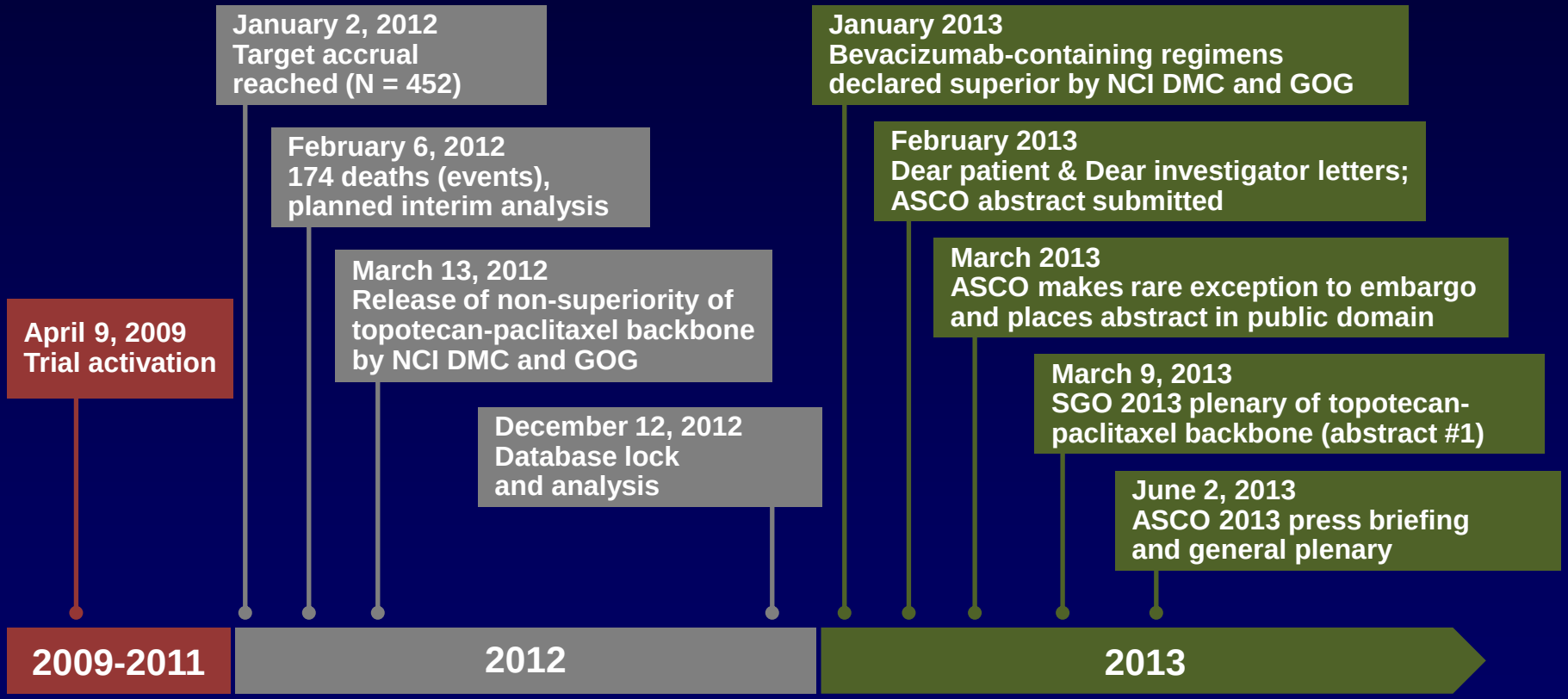
Tewari KS, et al. Presented at: The Society of Gynecologic Oncology's 2013 Annual Meeting on Women's Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

GOG 240.1: Conclusions

- This is the largest phase III randomized clinical trial in this population to complete accrual
- The substitution of topotecan for cisplatin does not result in improved OS
- The RR for the cisplatin-paclitaxel backbone remains high
- Topotecan-paclitaxel is a treatment alternative for this population
- Selection of either the Cis-Pac backbone or the Topo-Pac backbone should be predicated on toxicity screening/assessment, particularly in patients with prior Cis exposure

Tewari KS, et al. Presented at: The Society of Gynecologic Oncology's 2013 Annual Meeting on Women's Cancer; March 9-12, 2013: Los Angeles, California. Abstract 1.

GOG 240: Study Timeline, Part 2



ASCO, American Society of Clinical Oncology; chemoRx, chemotherapy treatment; DMC, data monitoring committee; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute.

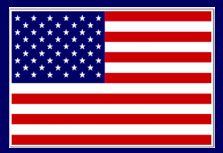
GOG 240.2

Incorporation of Bevacizumab in the Treatment of Recurrent and Metastatic Cervical Cancer

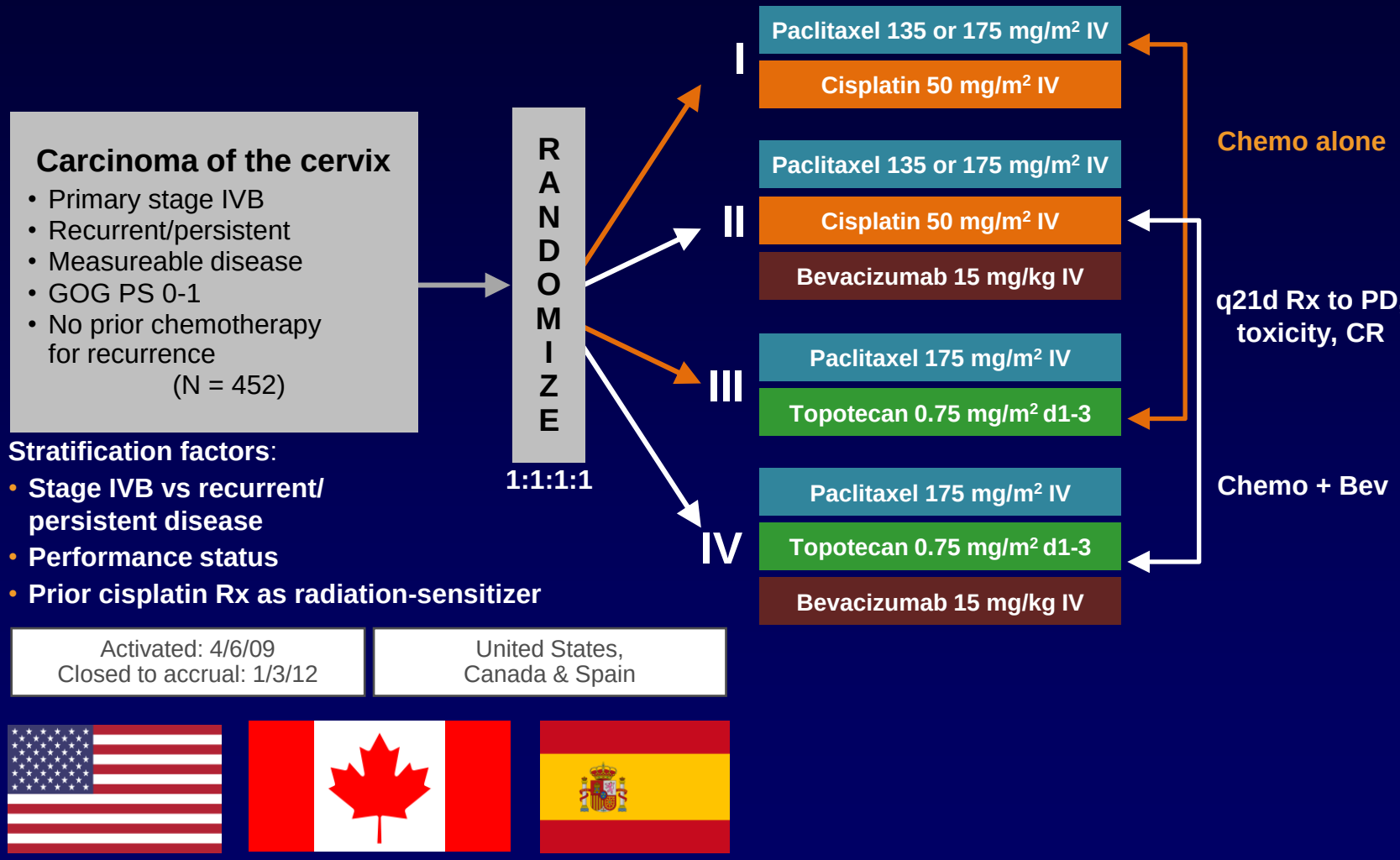
GOG 240: A Phase 3 Randomized Trial of the Gynecologic Oncology Group

KS Tewari, MW Sill, HJ Long 3rd, RT Penson, LM Ramondetta, LM Landrum, A Oaknin, TJ Reid, MM Leitao, HE Michael, BJ Monk

Presented at: ASCO Annual Meeting 2013
Abstract 3



GOG 240: 2 Schema



National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

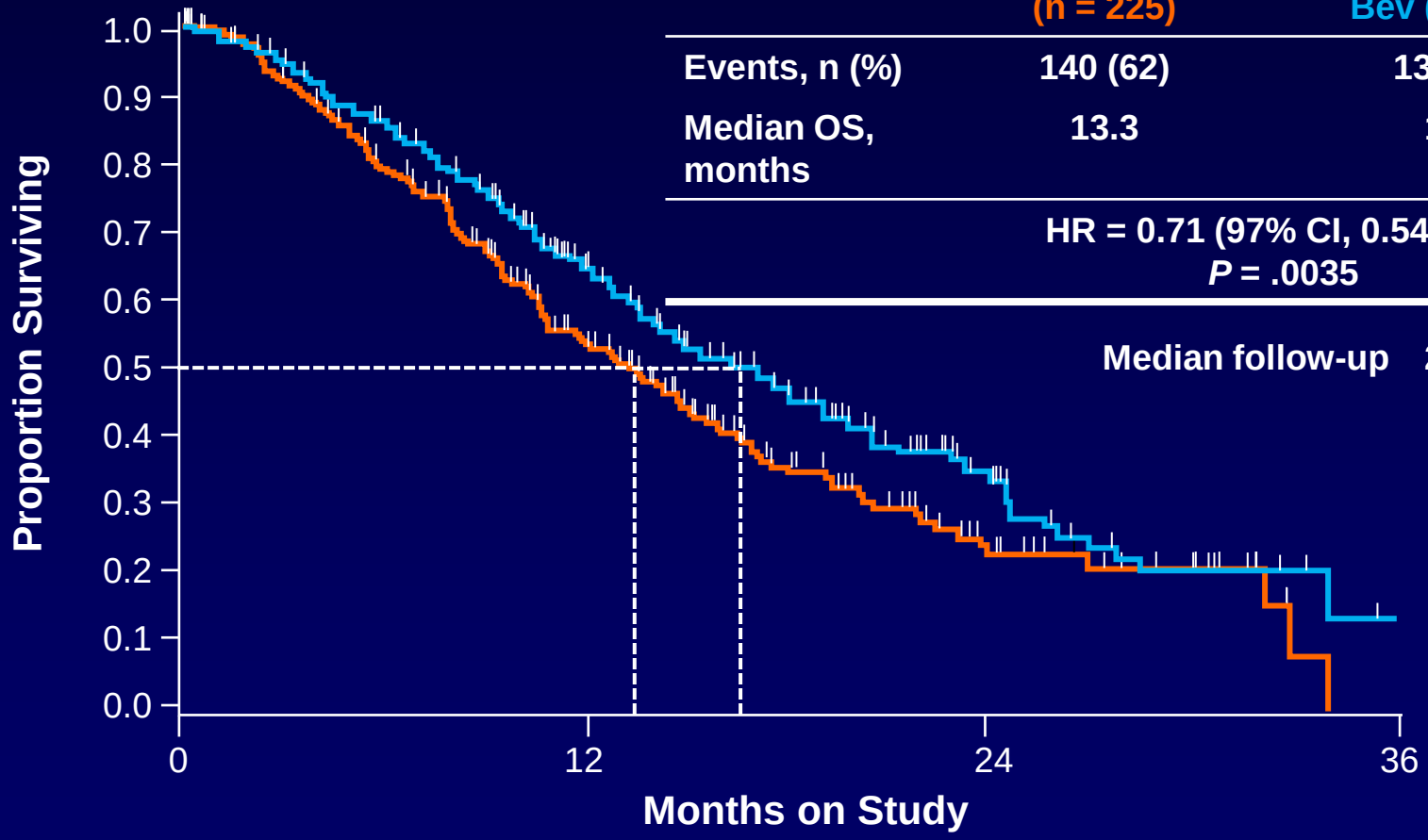
GOG 240.2: Demographics & Baseline Characteristics

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

Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

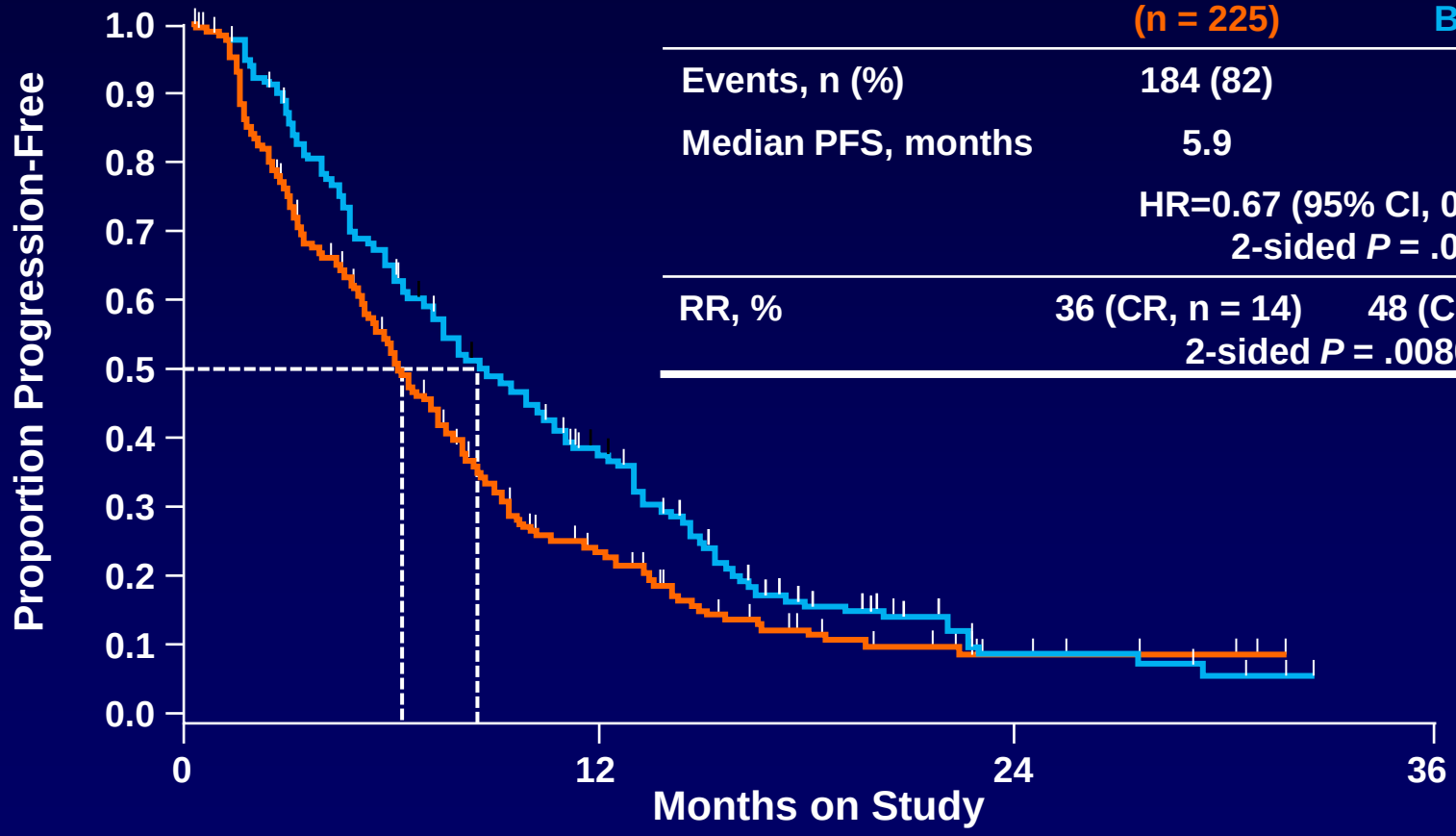
GOG 240.2: Second Interim Analysis OS for Chemo vs Chemo + Bev

	Chemotherapy (n = 225)	Chemotherapy + Bev (n = 227)
Events, n (%)	140 (62)	131 (58)
Median OS, months	13.3	17.0
	HR = 0.71 (97% CI, 0.54-0.94) *P* = .0035	
Median follow-up	20.8 months	



Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: Second Interim Analysis PFS for Chemo vs Chemo + Bev

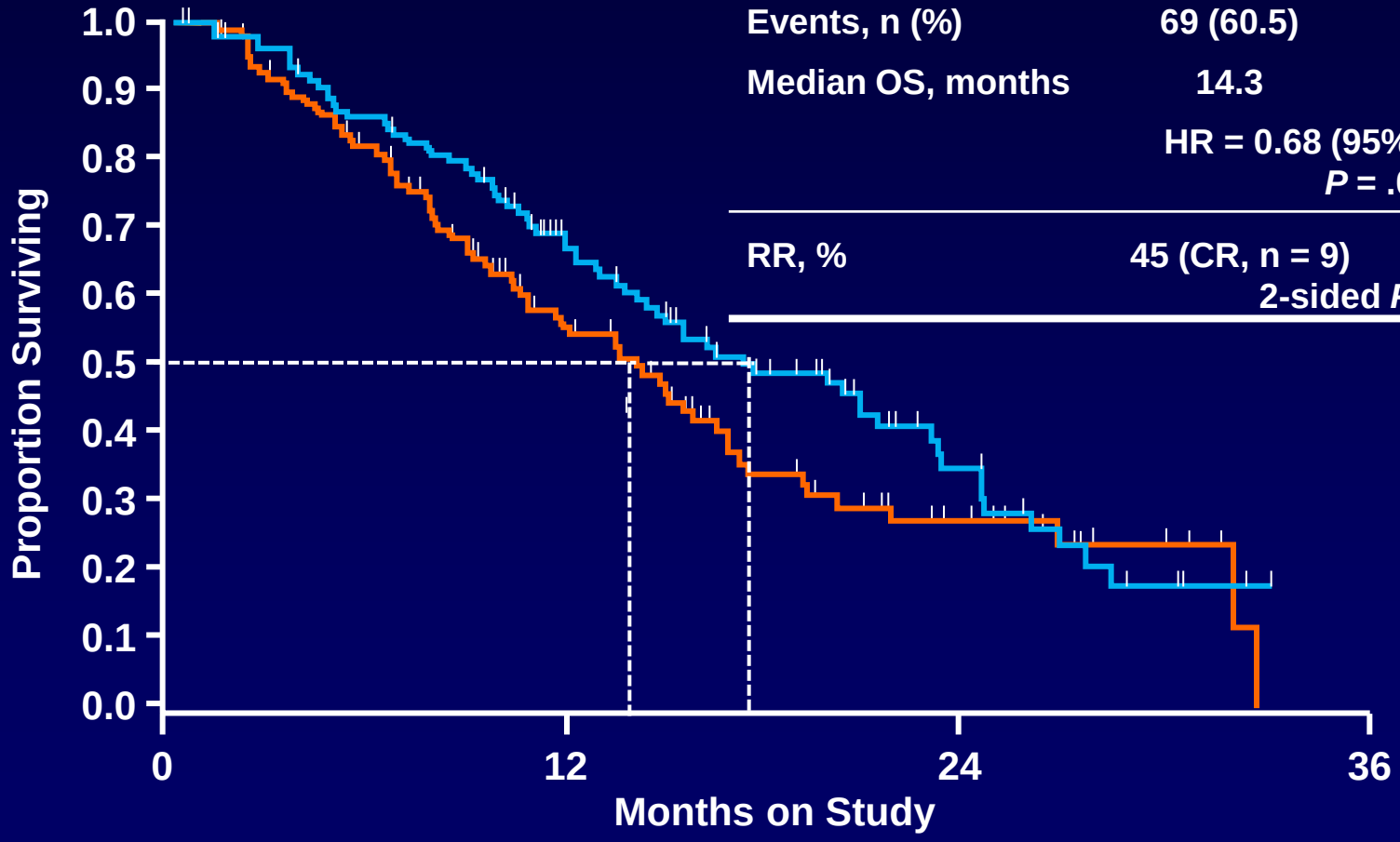


	Chemotherapy (n = 225)	Chemotherapy + Bev (n=227)
Events, n (%)	184 (82)	183 (81)
Median PFS, months	5.9	8.2
	HR=0.67 (95% CI, 0.54–0.82) 2-sided *P* = .0002	
RR, %	36 (CR, n = 14)	48 (CR, n = 28) 2-sided *P* = .00807

Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: OS for Cis + Pac vs Cis + Pac + Bev

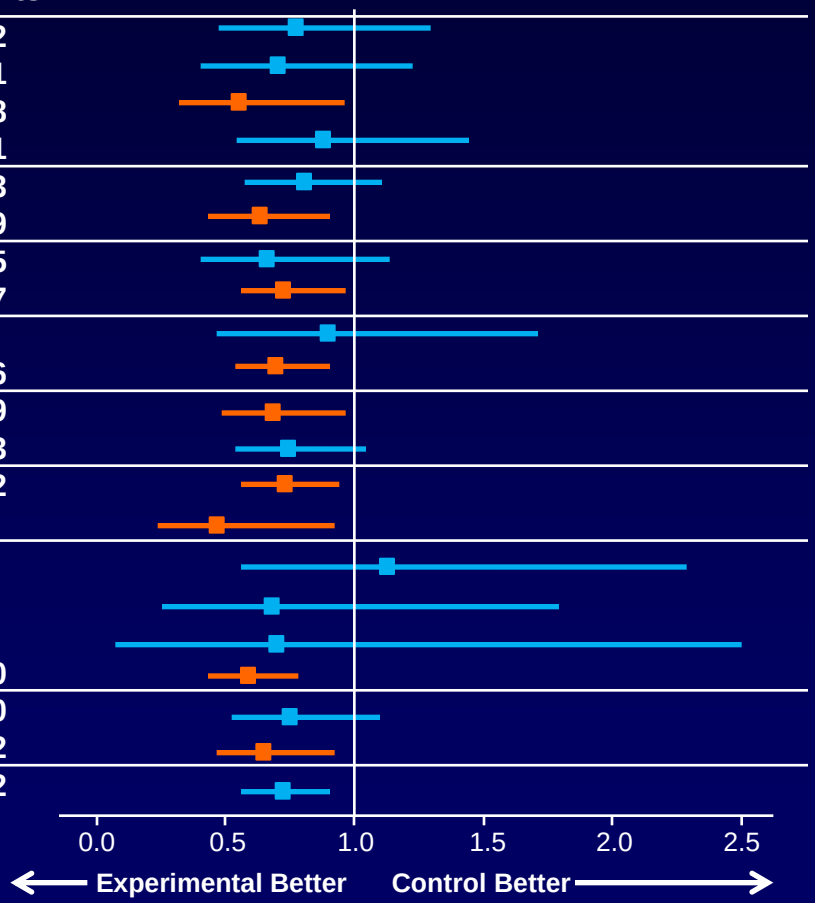
	Cis + Pac (n = 114)	Cis + Pac + Bev (n = 115)
Events, n (%)	69 (60.5)	67 (58.3)
Median OS, months	14.3	17.517.5
	HR = 0.68 (95% CI, 0.48-0.97) *P* = .0348	
RR, %	45 (CR, n = 9)	50 (CR, n = 17)
	2-sided *P* = .5090	



Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: OS and Prognostic Factors

Subgroup		No. of patients
Age	Age ≤40 years	112
	40 <age ≤48 years	111
	48 <age ≤56 years	108
	56 years <age	121
Performance status	0	263
	1	189
Prior platinum RT	No	115
	Yes	337
Disease status	Advanced	76
	Recurrent/persistent	376
Topotecan treatment	No	229
	Yes	223
Race	Not black	392
	Black	60
Histology	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic disease	No	210
	Yes	242
Overall		452



Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: Treatment Exposure and Specific Adverse Events (AEs)

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 ≥2)	96 (44)	114 (52)
GI fistula (grade ≥3)*	0 (0)	7 (3)
GI perforation (grade ≥3)	0 (0)	5 (2)
GU fistula (grade ≥3)*	1 (0)	6 (2)
Hypertension (grade ≥2)*	4 (2)	54 (25)
Proteinuria (grade ≥3)	0 (0)	4 (2)
Pain (grade ≥2)	62 (28)	71 (32)
Neutropenia (grade ≥4)*	57 (26)	78 (35)
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)
Thromboembolism (grade ≥3)*	3 (1)	18 (8)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0)	4 (1)
GU (grade ≥3)	1 (0)	6 (3)

*$P<.05$

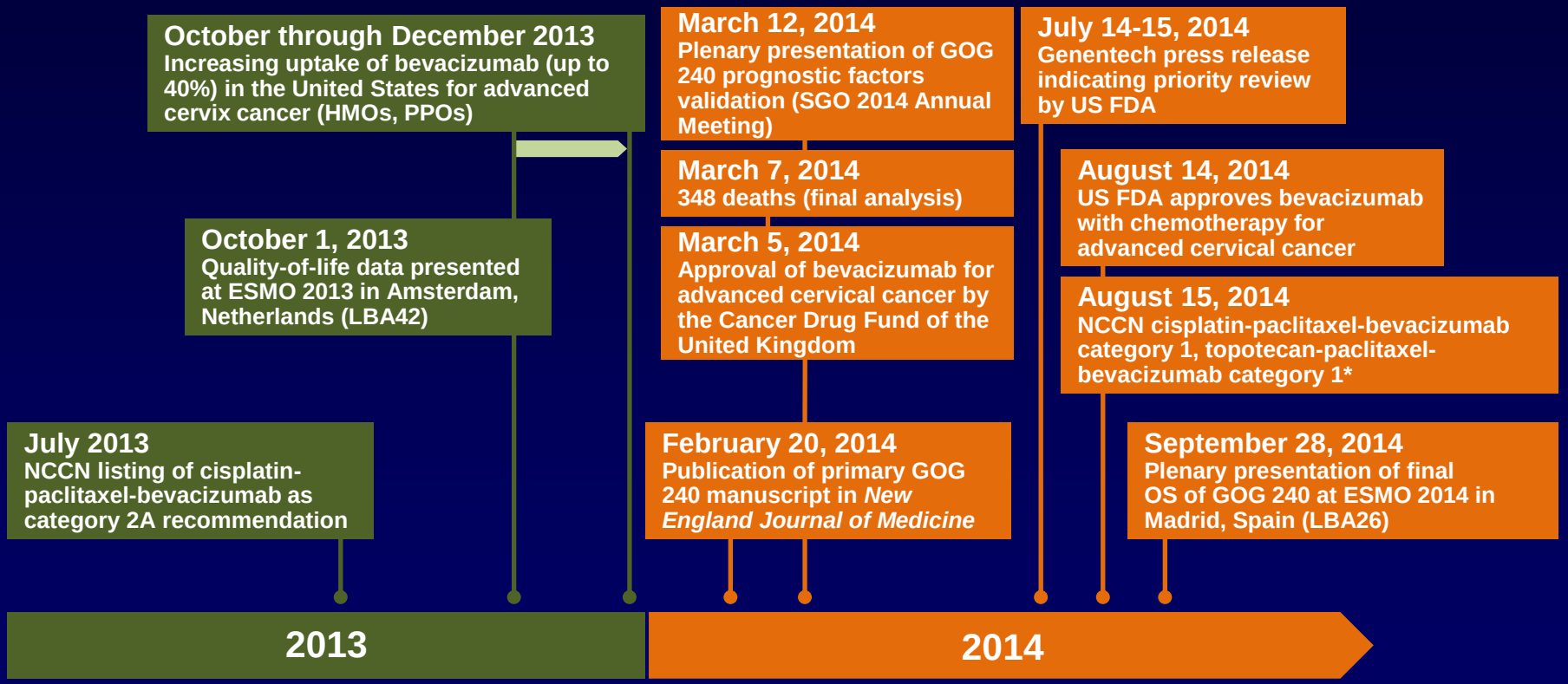
Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: 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 overall response rate 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
- First targeted agent to improve OS in a gynecologic cancer

Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240: Study Timeline, Part 3



HMO, health maintenance organization; PPO, preferred provider organization; US FDA, United States Food and Drug Administration

*Topotecan-paclitaxel-bevacizumab upgraded from NCCN category 2B to 1 (Sept 2014)

New England Journal of Medicine
February 20, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

ABSTRACT

Tewari KS, et al. *N Engl J Med*. 2014;370(8):734-743.

GOG 240.6

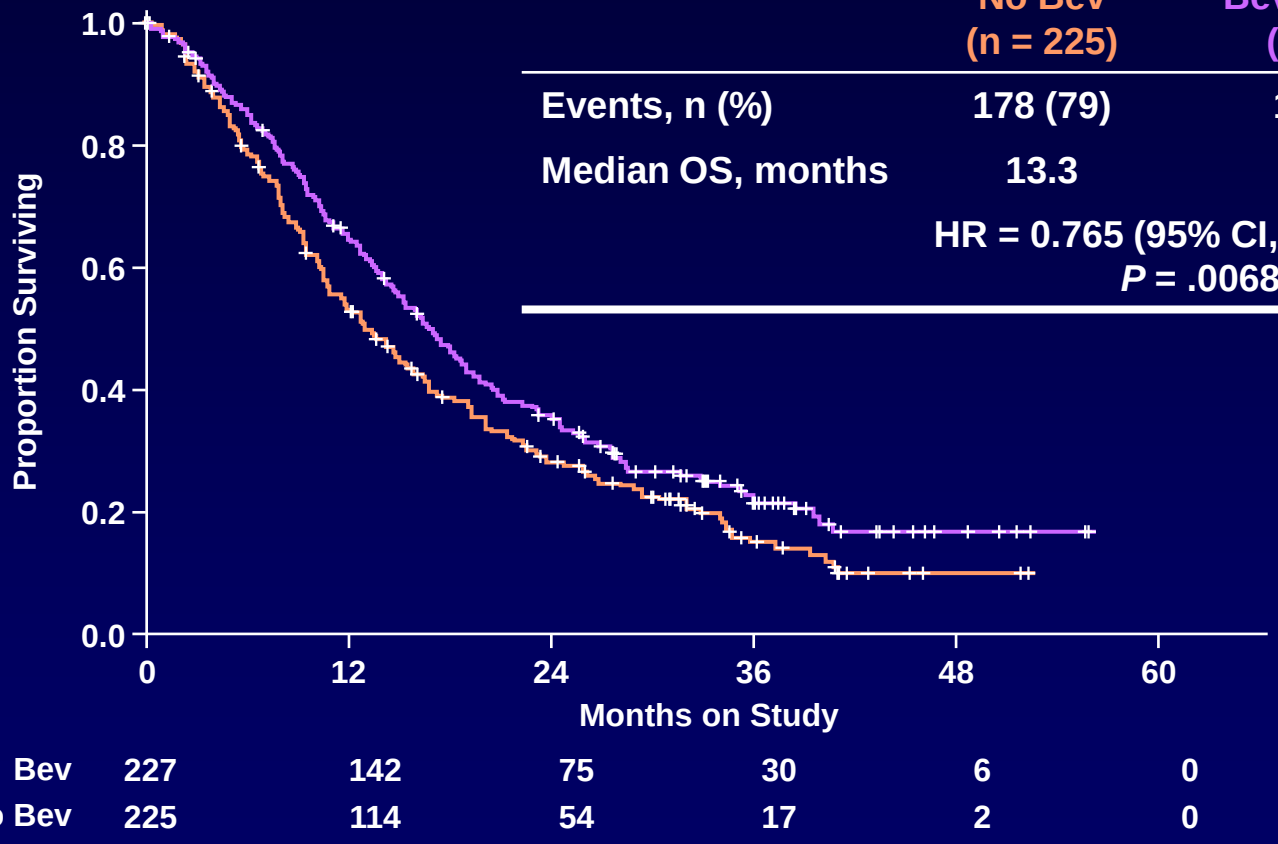
Final Protocol-Specified Overall Survival Analysis of the Phase III Randomized Trial of Chemotherapy With and Without Bevacizumab for Advanced Cervical Cancer: A NRG Oncology – Gynecologic Oncology Group Study

KS Tewari, MW Sill, RT Penson, H Huang, LM Ramondetta, LM Landrum, A Oaknin, TJ Reid, MM Leitao, H Michael, BJ Monk

Presented at: ESMO 2014
Abstract LBA26

GOG 240.6: Final Protocol-Specified OS ChemoRx vs ChemoRx Plus Bev

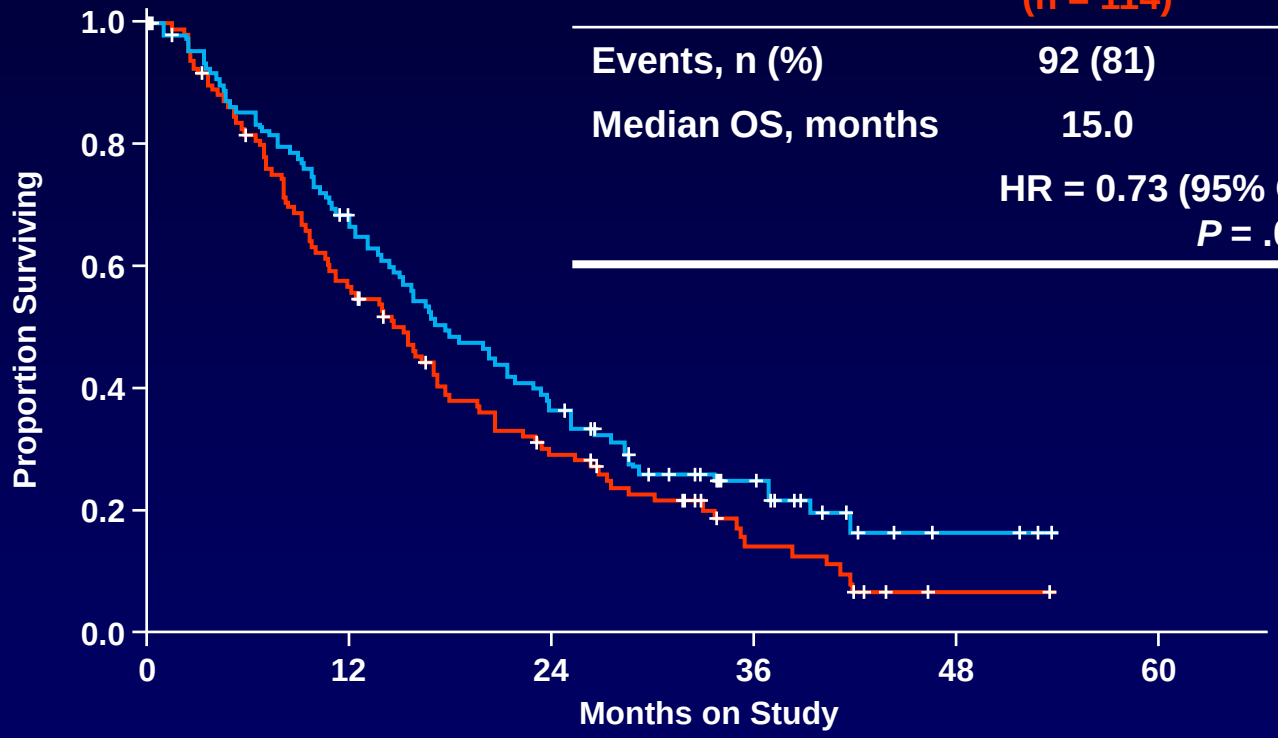
	No Bev (n = 225)	Bevacizumab (n = 227)
Events, n (%)	178 (79)	170 (75)
Median OS, months	13.3	16.8
	HR = 0.765 (95% CI, 0.62–0.95) *P* = .0068	



Tewari KS, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA26.

GOG 240.6: FINAL Protocol-Specified OS
Cis-Pac vs Cis-Pac-Bev

	Cis + Pac (n = 114)	Cis + Pac + Bev (n = 115)
Events, n (%)	92 (81)	83 (72)
Median OS, months	15.0	17.5
	HR = 0.73 (95% CI, 0.54–0.99) *P* = .04	



Tewari KS, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA26.

GOG 240: Study Team and Support

Study Design
- KS Tewari (PI & Study Chair)
- MW Sill (Statistician)
- BJ Monk (GOG Cervix Chair)
- HJ Long III (Med Onc) (1946-2013)

Co-Authors
- L Ramondetta, L Landrum, T Reid, M Leitao
- 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)

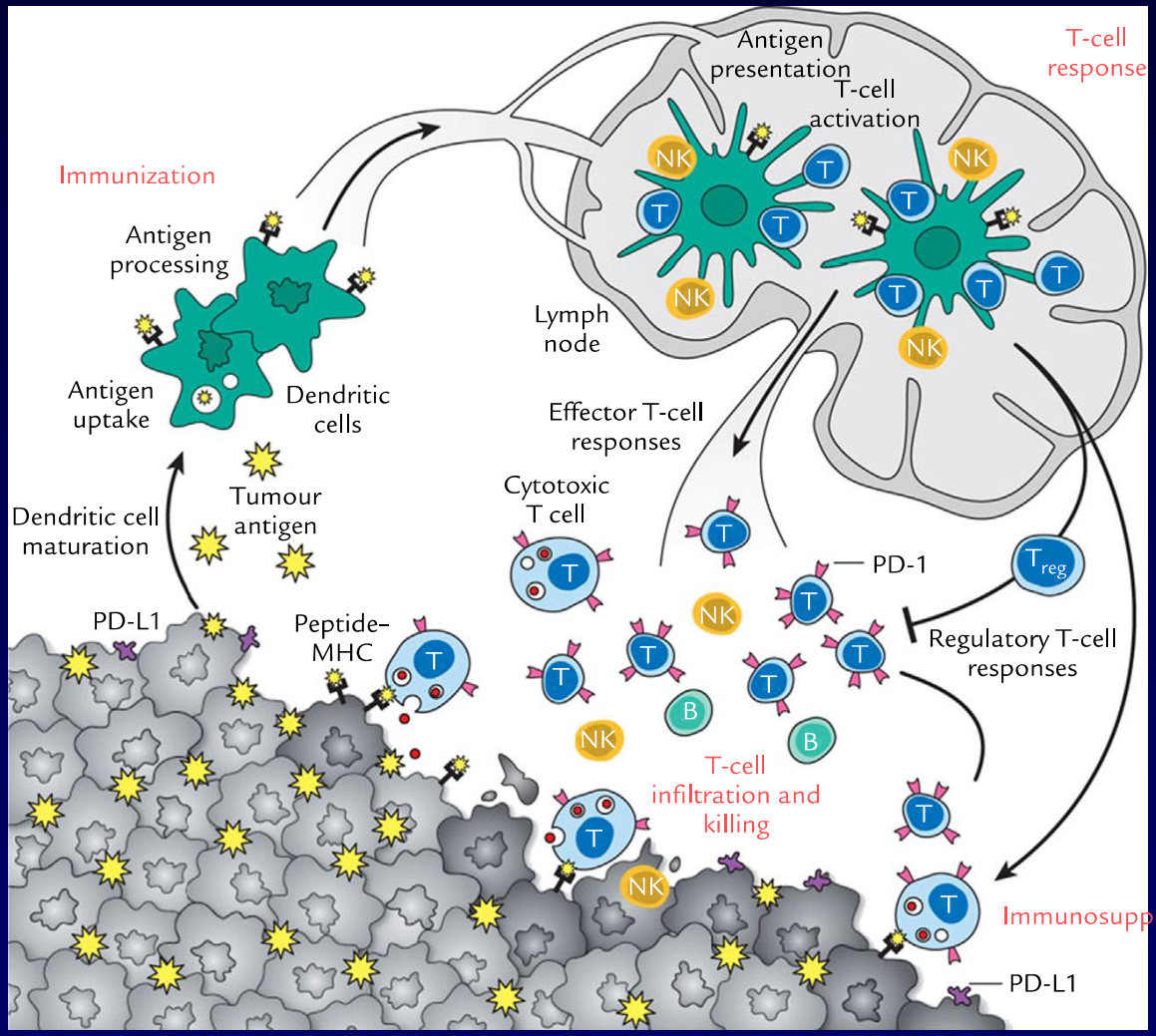
Genentech/Roche (USMA)
- K Look, A Husain, A Cannon

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

UC Irvine
- J Smith (Study Nurse)
- A Wallick (Data Management)

Immunotherapy: The Next Frontier



Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

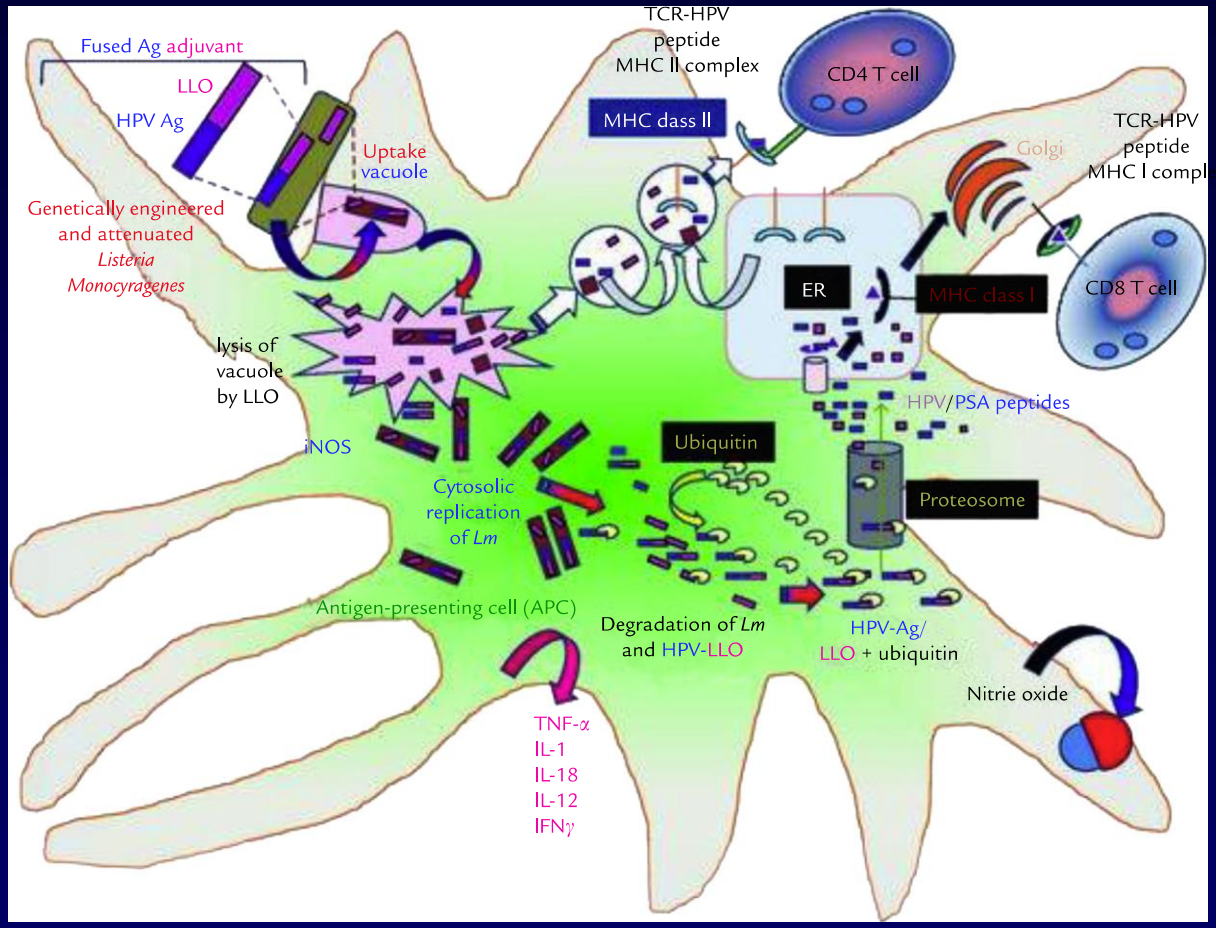
Immunotherapy: The Vaccines

Table II. Immunologic vaccines examined in Phase II clinical trials in patients with cervical cancer.

Type	Vaccine	Target
Live (bacterial and viral) vector–based vaccine	ADXS11-001 (bacterial)	HPV-16 E7 fusion protein
	TA-HPV (viral)	HPV-16 E6 and E7 peptide
Peptide	HLA-A*201	HPV-16 E7 peptide
Protein	SGN-00101	Fusion protein of HPV-16 E7
Nucleic acid	ZYC101a	HPV-16 E7 HLA-A2 restricted peptide
	VGV-3100a	Plasmid targeting HPV-16 and HPV-18 E6 and E7

Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

ADXS-HPV (ADXs11-001)



Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

Advaxis Technologies

***Lm*-LLO proprietary cancer immunotherapy platform technology**

- **Live attenuated bacteria stimulate the immune system to view tumor as a bacterial infection for elimination**
- **Alters the tumor microenvironment by increasing cells beneficial in fighting tumors**

3 immunotherapies in clinical development

ADXS-HPV (ADXS-HPV): Plan to initiate pivotal phase III program, 2014

- **Long-term survival and objective tumor responses in 109 patients with recurrent cervical cancer**
- **Conducted EOP2 with FDA in July and planning to file SPA in November 2014**
- **PD-L1 combination trial with AstraZeneca/MedImmune to initiate Q1 2015**

ADXS-cHER2 (ADXS31-164): Plan to file IND for HER2 overexpressing cancers , 2014

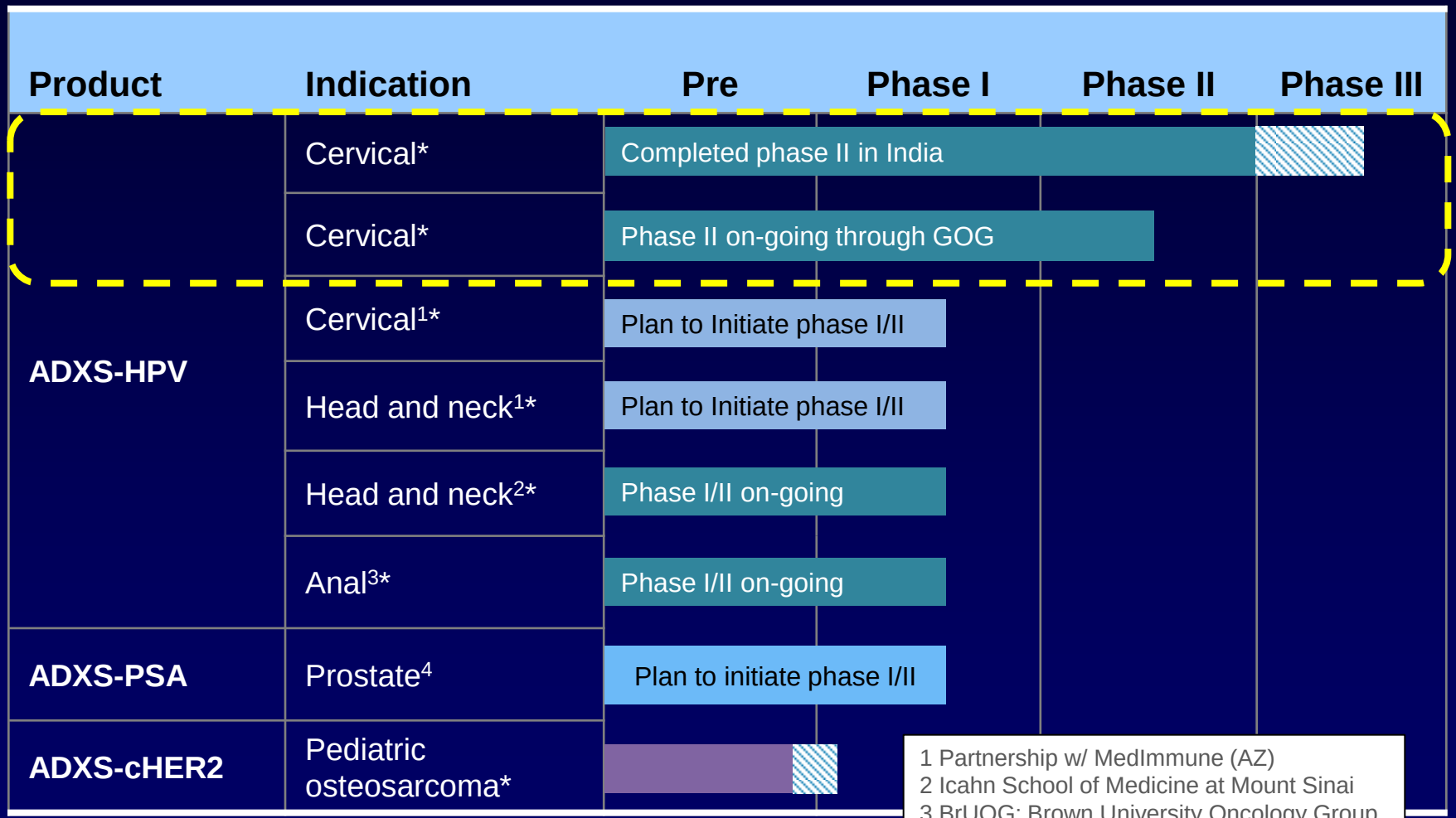
- **Statistically significant survival data in canine osteosarcoma, licensed to Aratana Therapeutics**
- **Provides rationale to pursue HER2-overexpressing cancer in humans**

ADXS-PSA (ADXS-PSA): Plan to file IND and initiate phase I/II in prostate cancer, 2014

- **PD-1 Combination trial with Merck to initiate Q1 2015**

http://www.advaxis.com

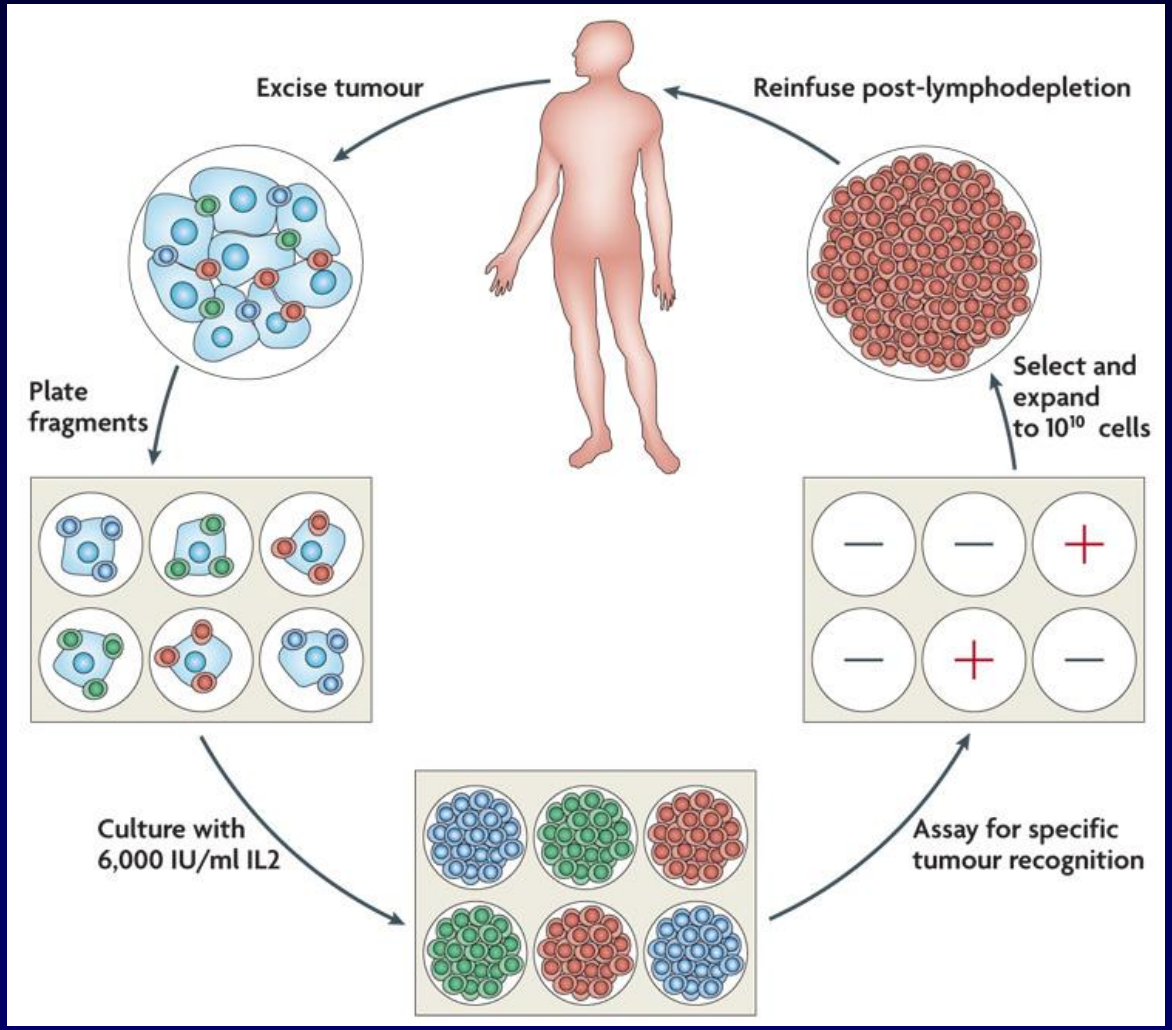
Advaxis Clinical Pipeline



Projected 2015

1 Partnership w/ MedImmune (AZ)
2 Icahn School of Medicine at Mount Sinai
3 BrUOG: Brown University Oncology Group
4 Partnership w/ Merck
*Orphan drug designation

Adoptive T Cell Transfer Using Tumor-infiltrating Lymphocytes



Rosenberg SA, et al. *Nat Rev Cancer*. 2008;8(4):299-308.

HPV-Targeted Tumor-Infiltrating Lymphocytes for Metastatic Cervical Cancer

Hinrichs CS, Stevanović S, Draper L, Somerville R, Wunderlich J, Restifo NP, Sherry R, Phan GQ, Kammula US, Yang JC, Rosenberg SA

Presented at: ASCO Annual Meeting 2014

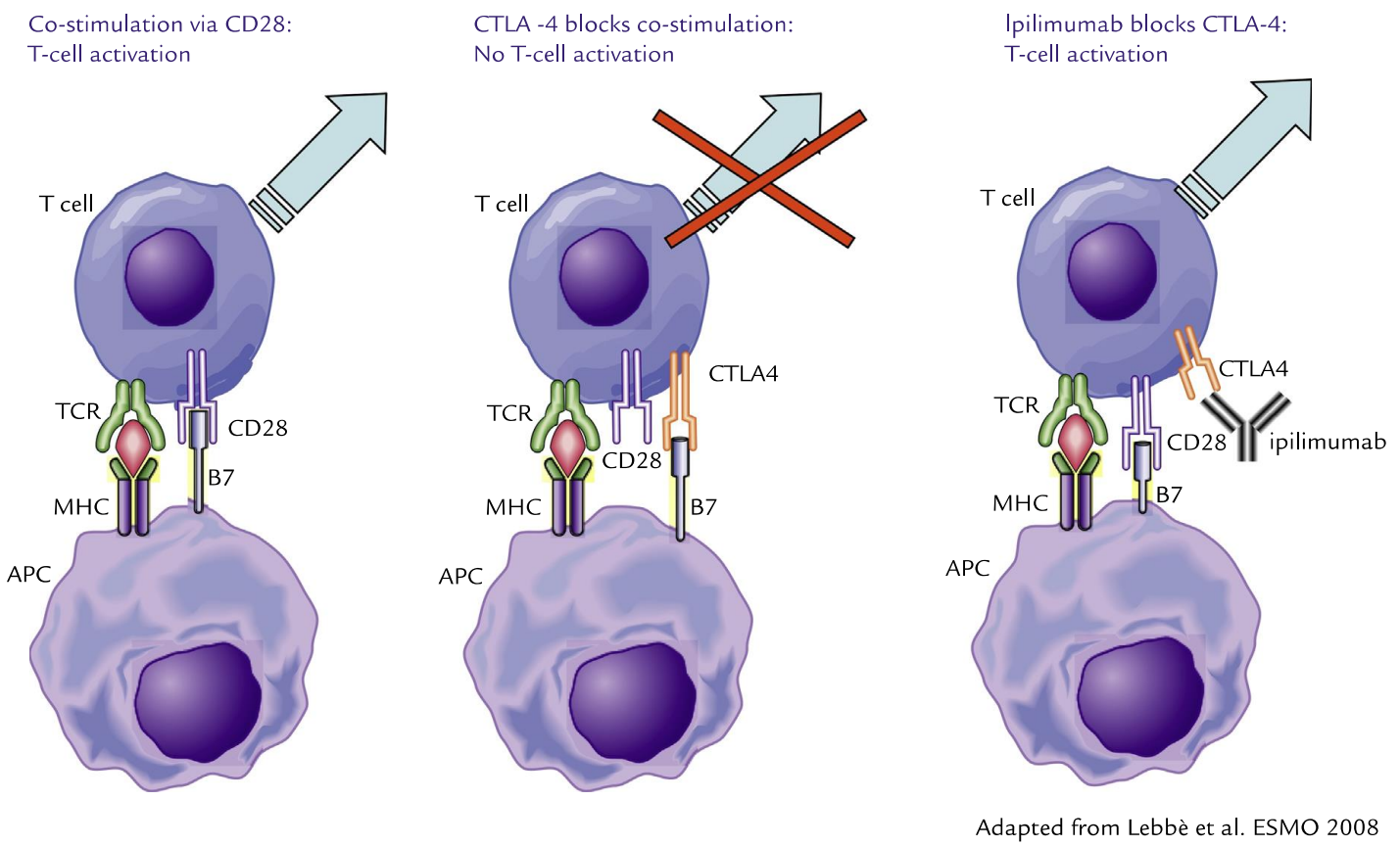
Abstract LBA3008

Patient Characteristics

Patient	Age	Histology	HPV type	Prior systemic therapy	Cell dose ($x10^9$)	Response (duration in months)*
1	30	Adeno-squamous	HPV-18	Cisplatin	101	PD
2	53	Squamous	HPV-18	Cisplatin, paclitaxel, carboplatin, topotecan, ixabepilone, phase I trial	126	PR (3)
3	36	Squamous	HPV-16	Bleomycin, vincristine, cisplatin, gemcitabine, topotecan, paclitaxel	152	CR (22+)
4	55	Squamous	HPV-16	Carboplatin, 5-FU, irinotecan	80	PD
5	44	Squamous	HPV-18	Cisplatin	90	PD
6	36	Adeno	HPV-18	Cisplatin	75	CR (15+)
7	59	Adeno	HPV-18	Cisplatin, carboplatin, paclitaxel, bevacizumab	33	PD
8	31	Adeno-squamous	HPV-18	Cisplatin, paclitaxel	46	PD
9	37	Adeno	HPV-18	Carboplatin, paclitaxel, ipilimumab	70	PD
* Duration measured in months from cell infusion						

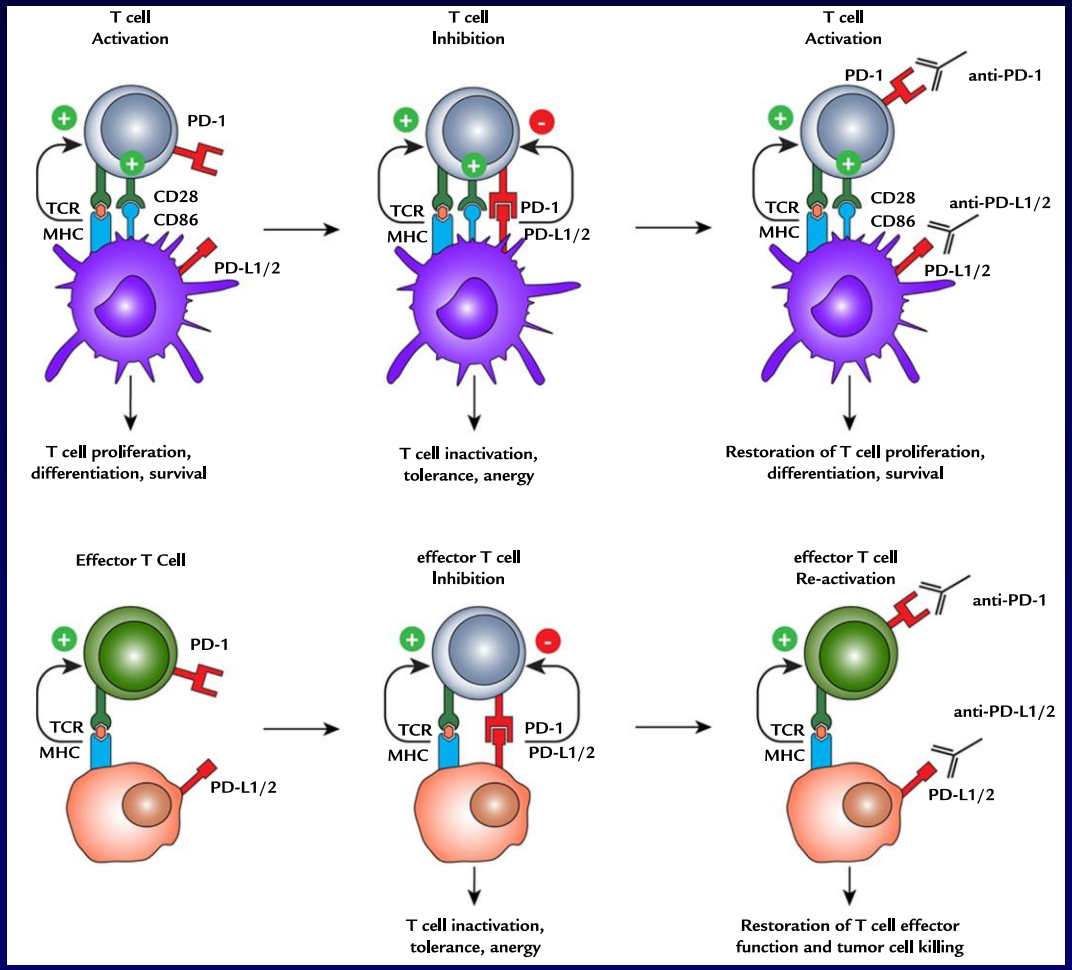
Hinrichs CS, et al. *J Clin Oncol*. . 2014;32(5s): Abstract LBA3008.

Checkpoint Inhibition: Overcoming Immune Tolerance



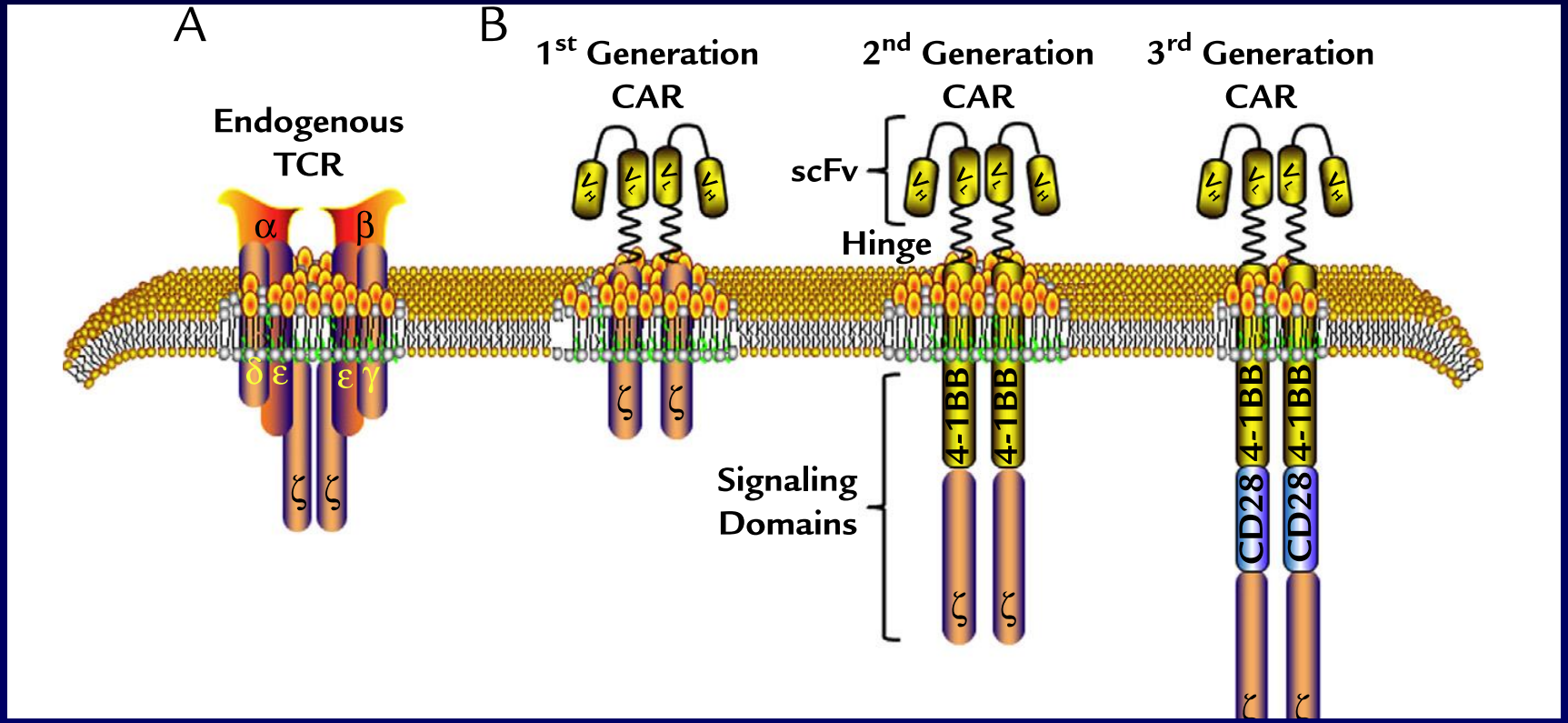
Lebbe C, et al. Presented at: 33rd European Society for Medical Oncology Congress; September 12-16, 2008; Stockholm, Sweden.

Monoclonal Antibodies Directed Against PD-1, or Its Ligands, Promote T cell Activation by Shifting the Balance of Signals Delivered by the DC from Suppressive to Activating



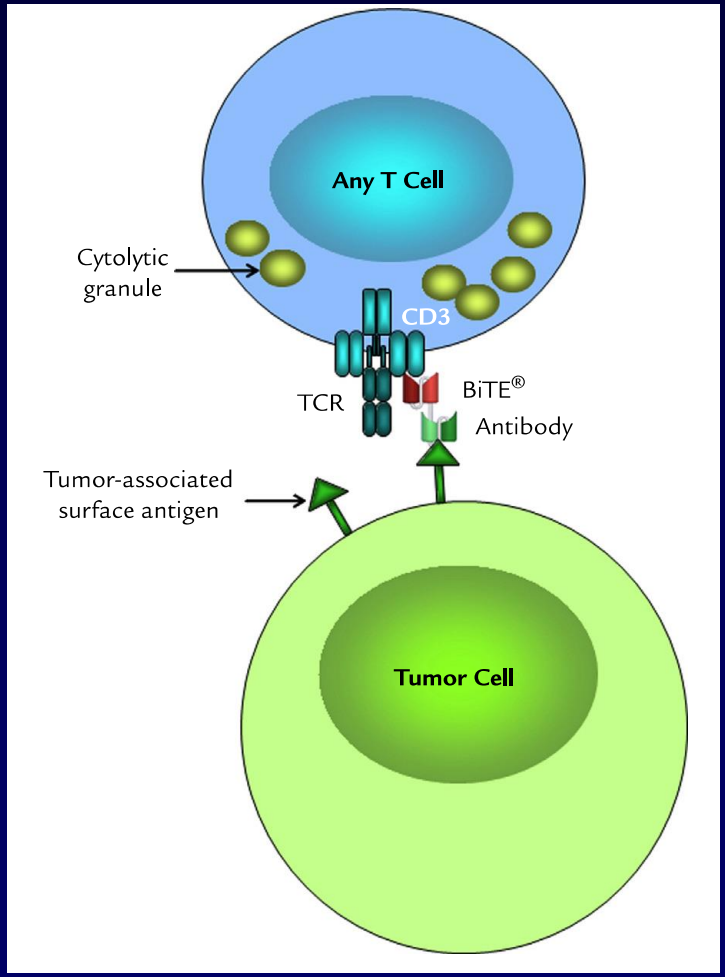
Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

T cells Engineered to Express Chimeric Antigen Receptors or "CARs" That Recognize Surface Antigens in an MHC-Unrestricted Manner



Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

BiTE Molecule Forming Cytolytic Synapse Between Tumor Cell Expressing Target of Interest and T cell



Eskander RN, et al. *Clinical Therapeutics*. 2015;37(1).

Thank You

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2015

Progress and Controversies in Gynecologic Oncology Conference