TARGETED THERAPYIN CERVICAL CANCER

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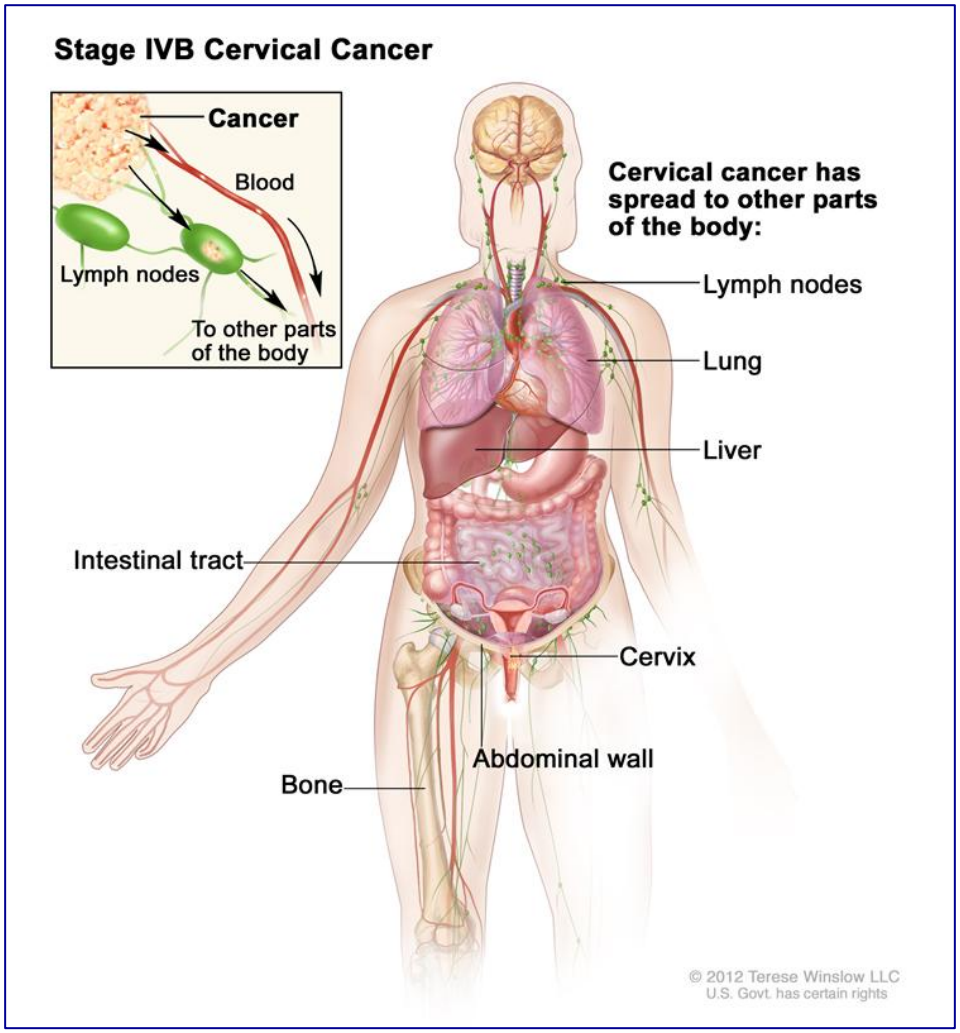
Verbal Disclosure

- My institution has received grants for me from Amgen, Genentech, Eli Lilly, Array, TESARO Inc., Morphotek, and Janssen/Johnson & Johnson.
- I have received honoraria for speakers' bureaus from Genentech, Roche, AstraZeneca, Myriad, and Janssen/Johnson & Johnson.
- I have received honoraria for my consulting with Merck, TESARO Inc., Gradalis, Advaxis, Amgen, Bayer, Insys, Clovis, Mateon (formally OxiGENE), Roche, Genentech, AstraZeneca, Pfizer and PPD.

- I agree that content of this presentation will be well balanced, unbiased, and evidence-based. Opinions that are not supported by evidence, or are supported by limited or preliminary evidence will be so identified.

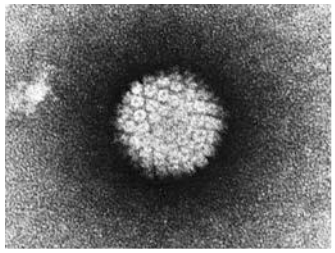
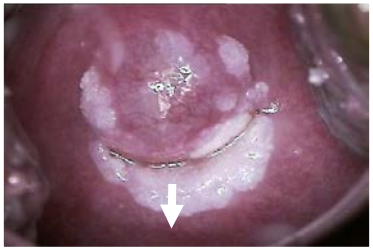
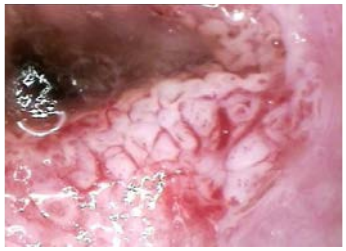
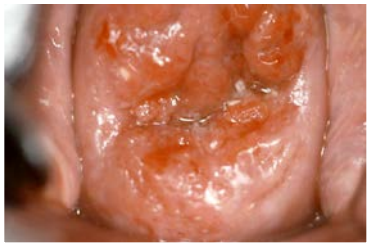
Recurrent/Persistent and Metastatic Disease:
A HIGH UNMET CLINICAL NEED!



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]

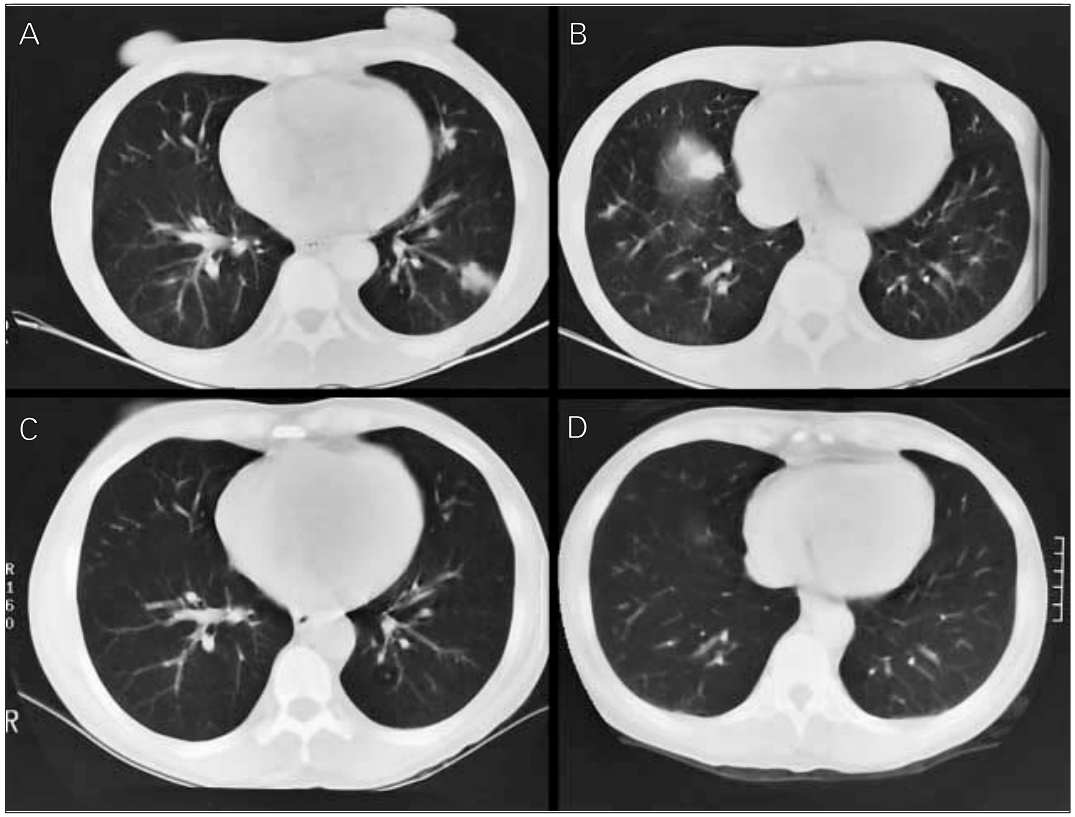





Colposcopy demonstrates abnormal vasculature and angiogenesis dependent progression of cervical neoplasia

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.

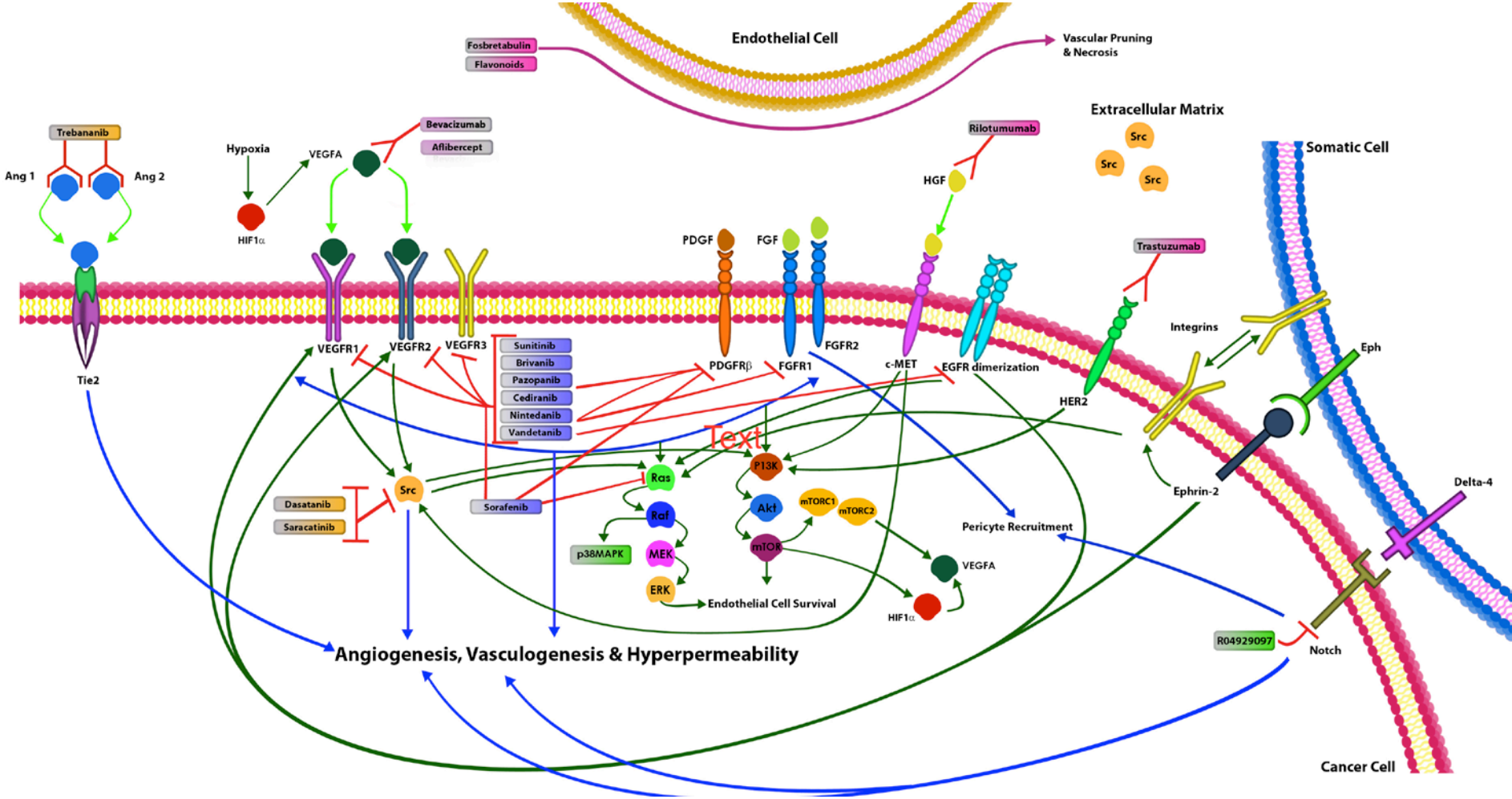
Complete Remission of Metastatic Cervical Cancer With the Angiogenesis Inhibitor TNP-470



- ✓ **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.

The Angiogenesis Map



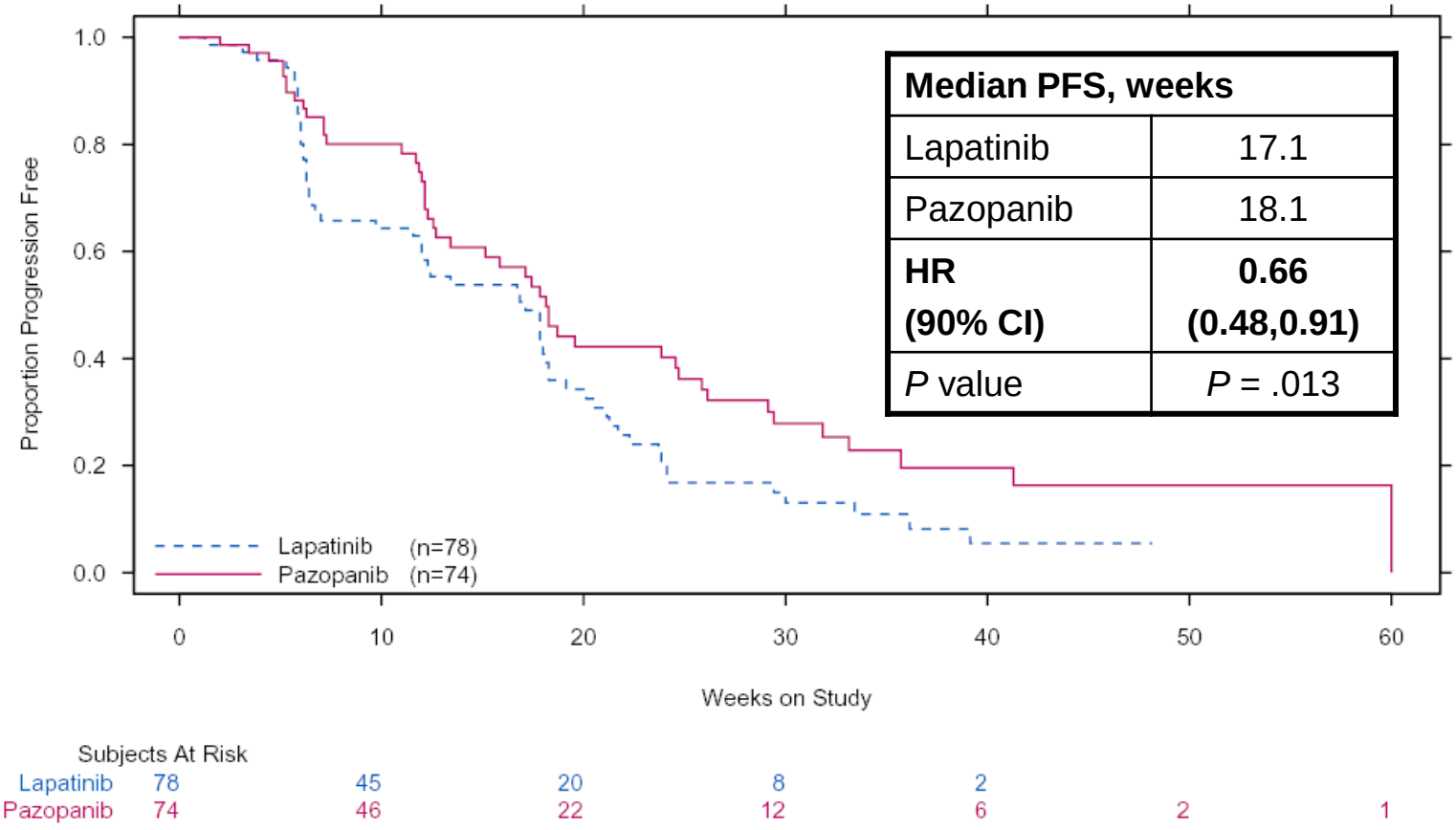
Liu FW, et al. *Oncology.* 2015;29(5):350-360.

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

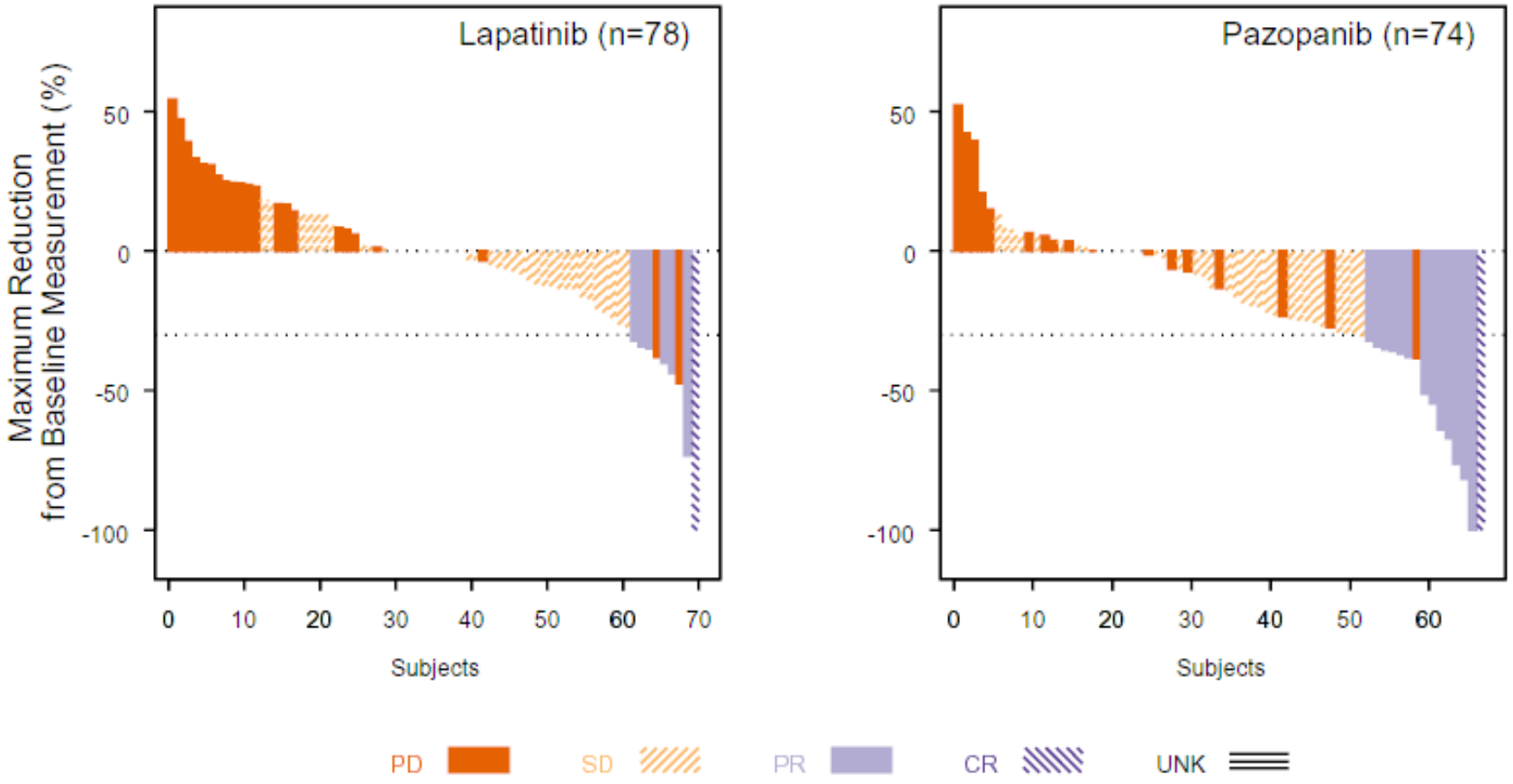
Monk BJ, et al *J Clin Oncol*. 2010;28(22):3562-3569.

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

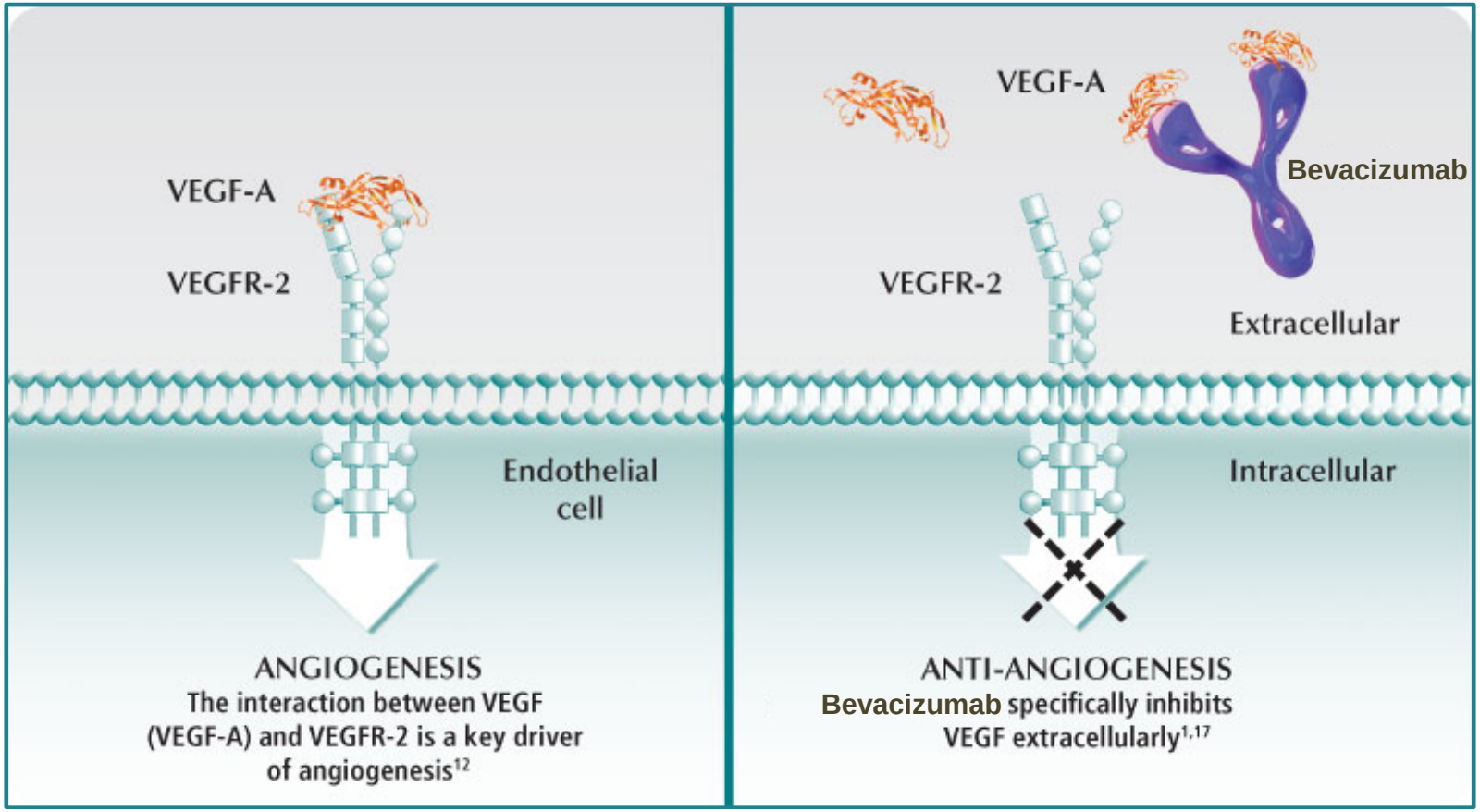
Maximum decrease in target lesion diameter: Lapatinib vs Pazopanib



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

GOG 227C

Phase II Bevacizumab, Recurrent Cervical Cancer

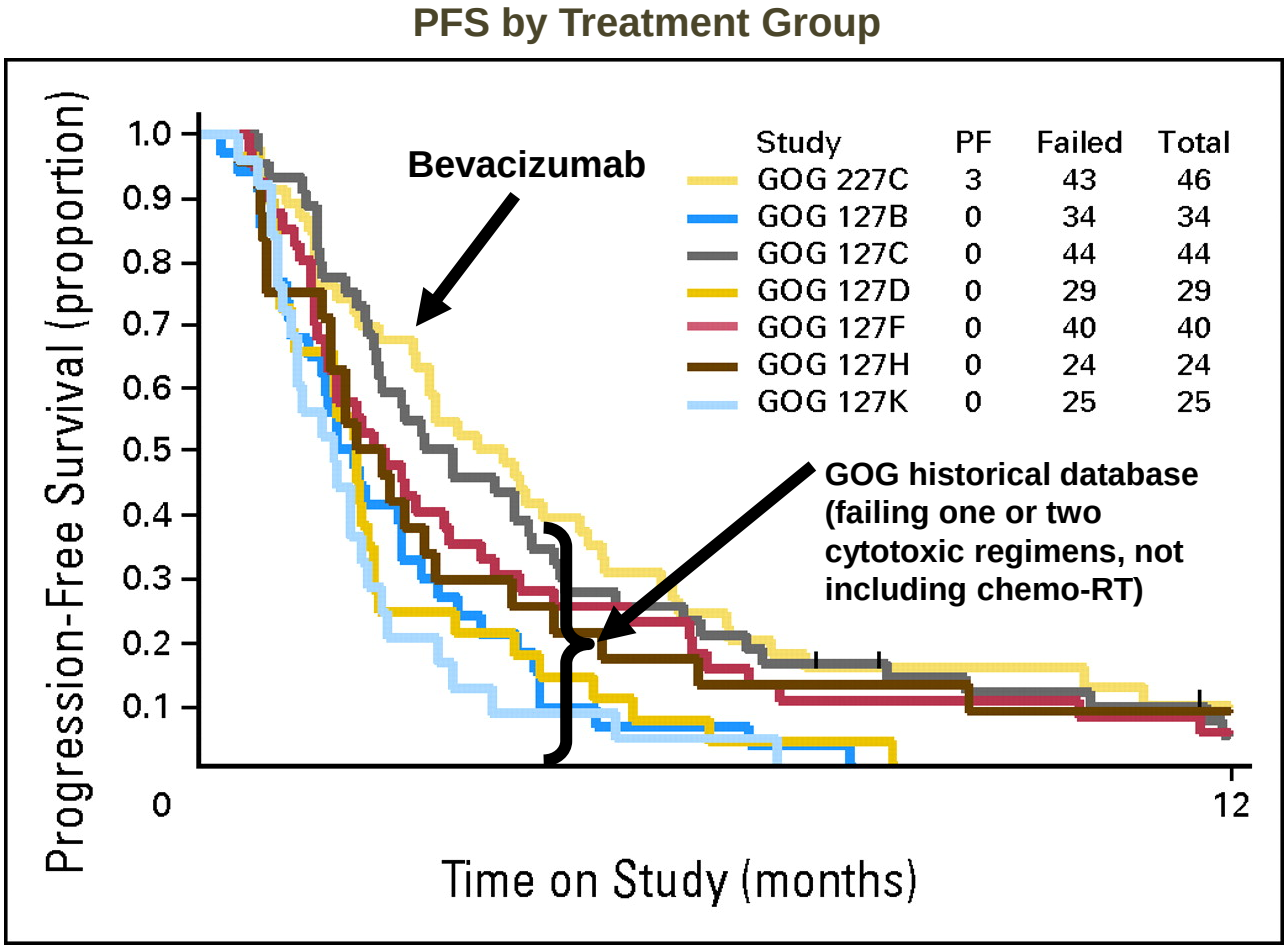


Monk BJ, et al. *J Clin Oncol.* 2009;27(7):1069-1074.

GOG 227C

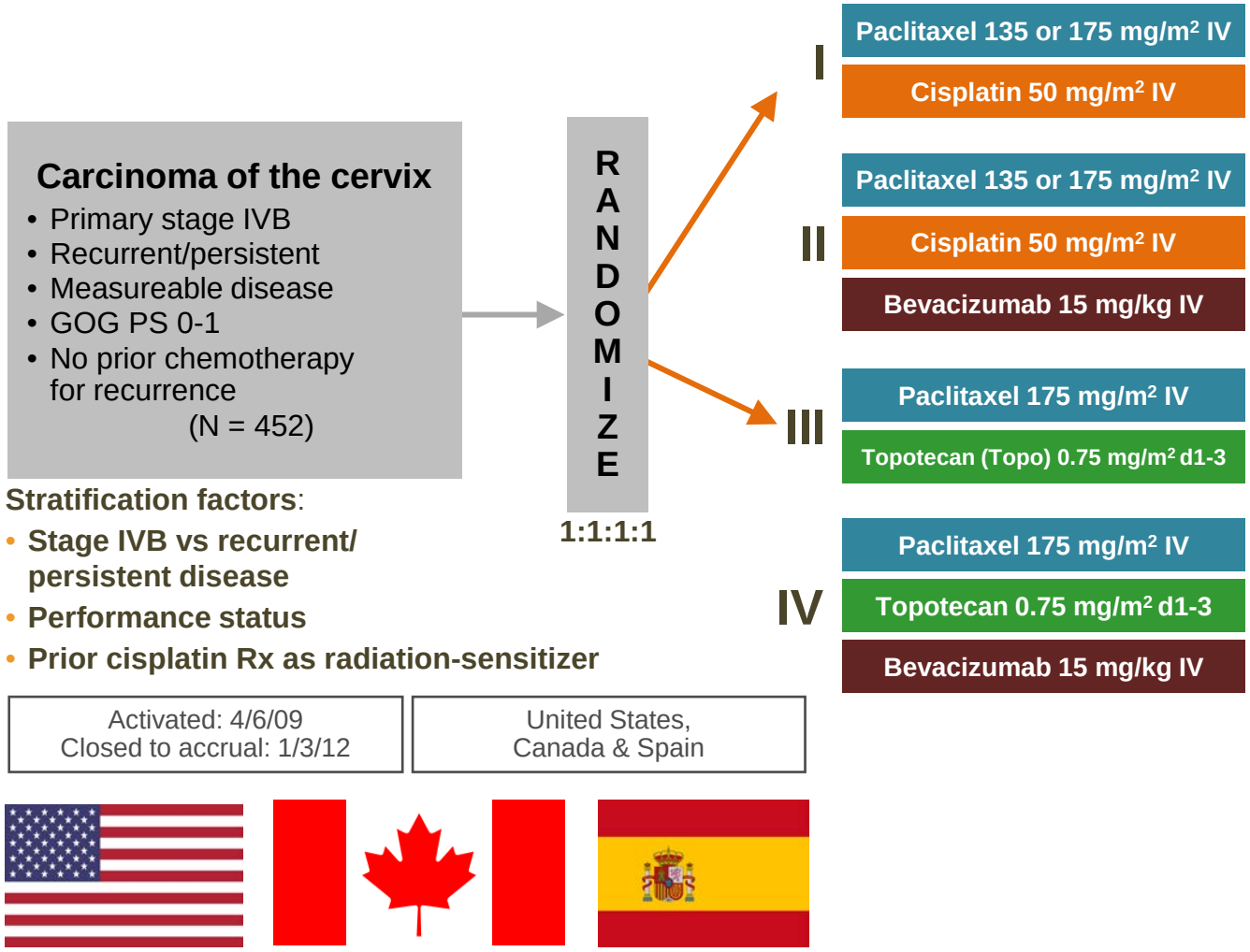
Phase II Bevacizumab, Recurrent Cervical Cancer

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



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: Publications

- GOG 240.1: Non-platinum chemotherapy chemotherapy backbone.
- GOG 240.2: Primary bevacizumab endpoint. *N Engl J Med.* 2014;370(8):734-743.
- GOG 240.3: Patient reported outcomes. *Lancet Oncol.* 2015;16(3):301-311.
- GOG 240.4: Moore prognostic criteria. *Clin Cancer Res.* 2015;21(24):5480-5487.
- GOG 240.5: Circulating tumor cells.
- GOG 240.6: Prognostic significance of smoking.
- GOG 240.7: Mature survival.
- GOG 240.8: Prognostic significance tumor histology.
- GOG 240.9: Fistula data.
- GOG 240.10: Complete responder data.
- GOG 240.11: Cost-effectiveness. *Gynecol Oncol.* 2015;137(3):490-496.

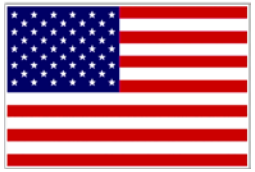
GOG 240.1

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

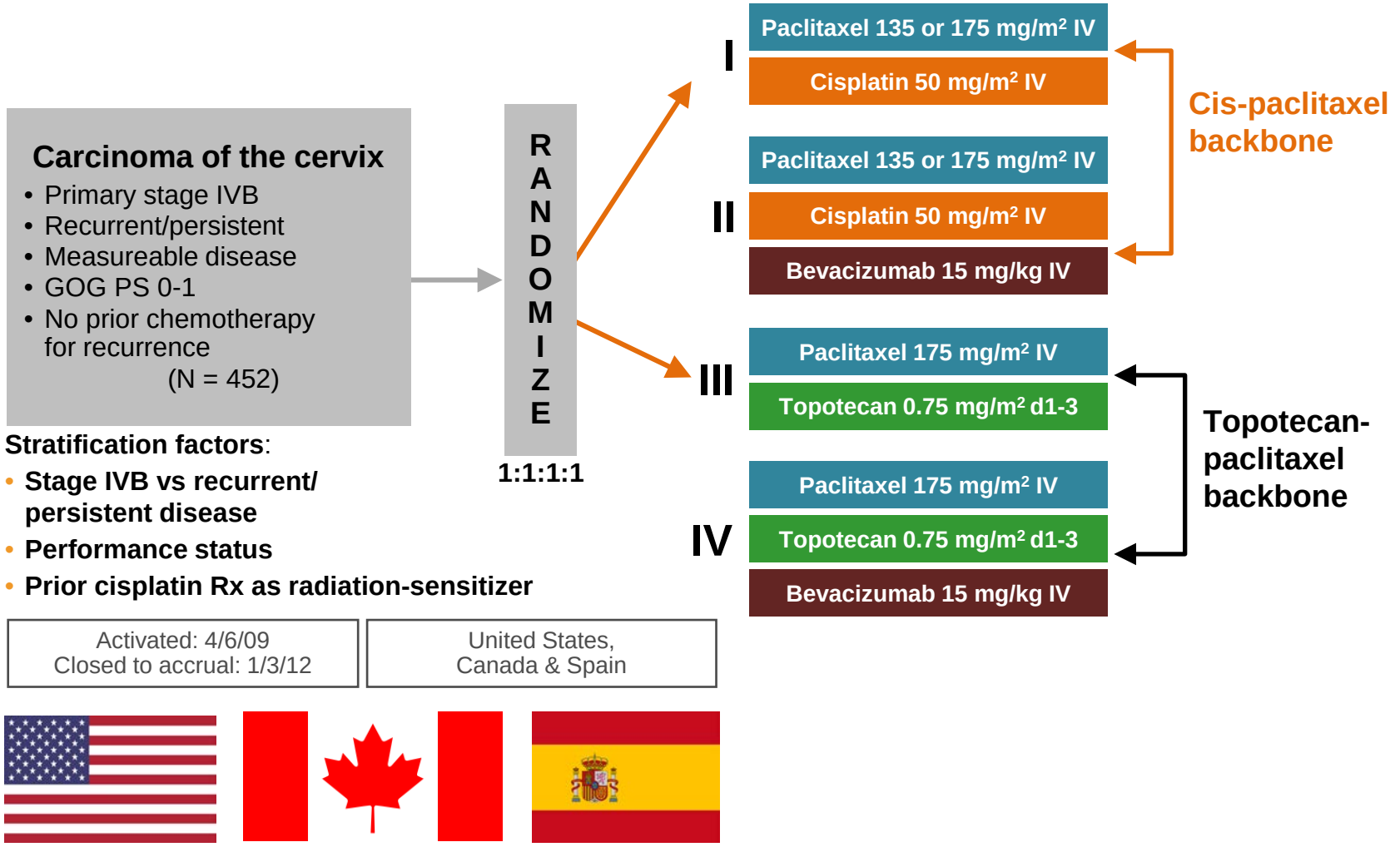
KS Tewari, M Sill, HJ Long III, L Ramondetta, L Landrum, A Oaknin, T Reid, M Leitao, H Michael, BJ Monk

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%	.308
Adenocarcinoma, unspecified	20%	21%	
White	78%	77%	.800
African American	13%	13%	
Asian	5%	4%	
Pacific Islander	0.4%	0.00	
Recurrent	75%	69%	.298
Persistent	9%	14%	
Advanced	16%	17%	
PS 0	57%	59%	.703
PS 1	43%	41%	
Prior platinum	76%	74%	.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.

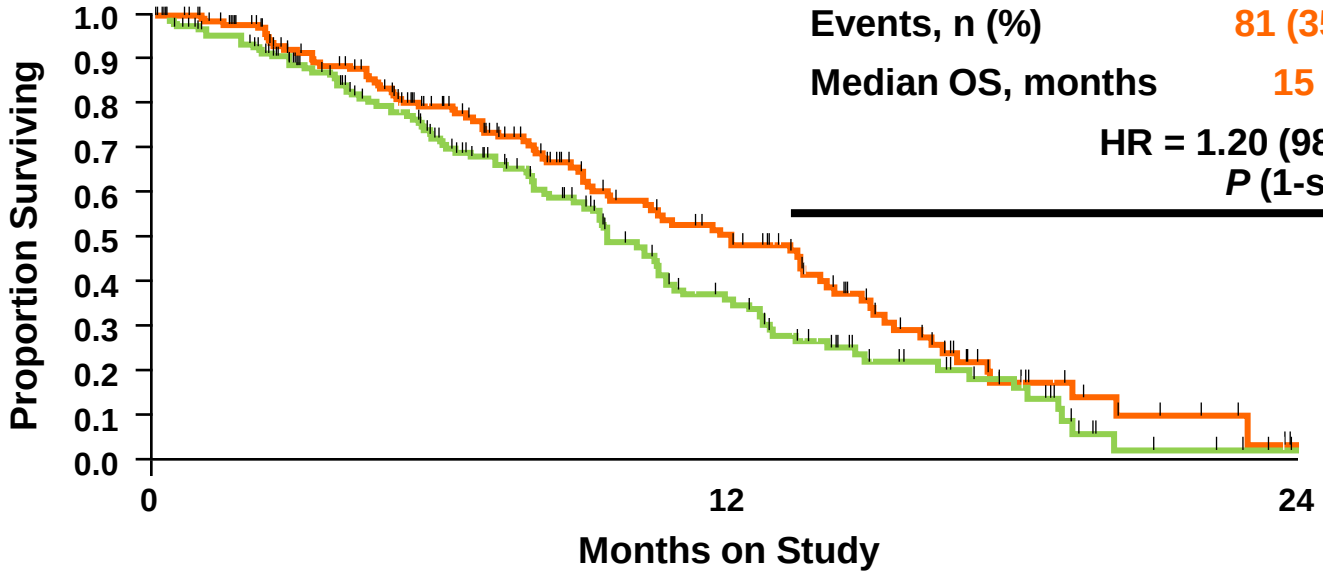
GOG 240.1: Results
Planned Interim Analysis

- **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 240.2

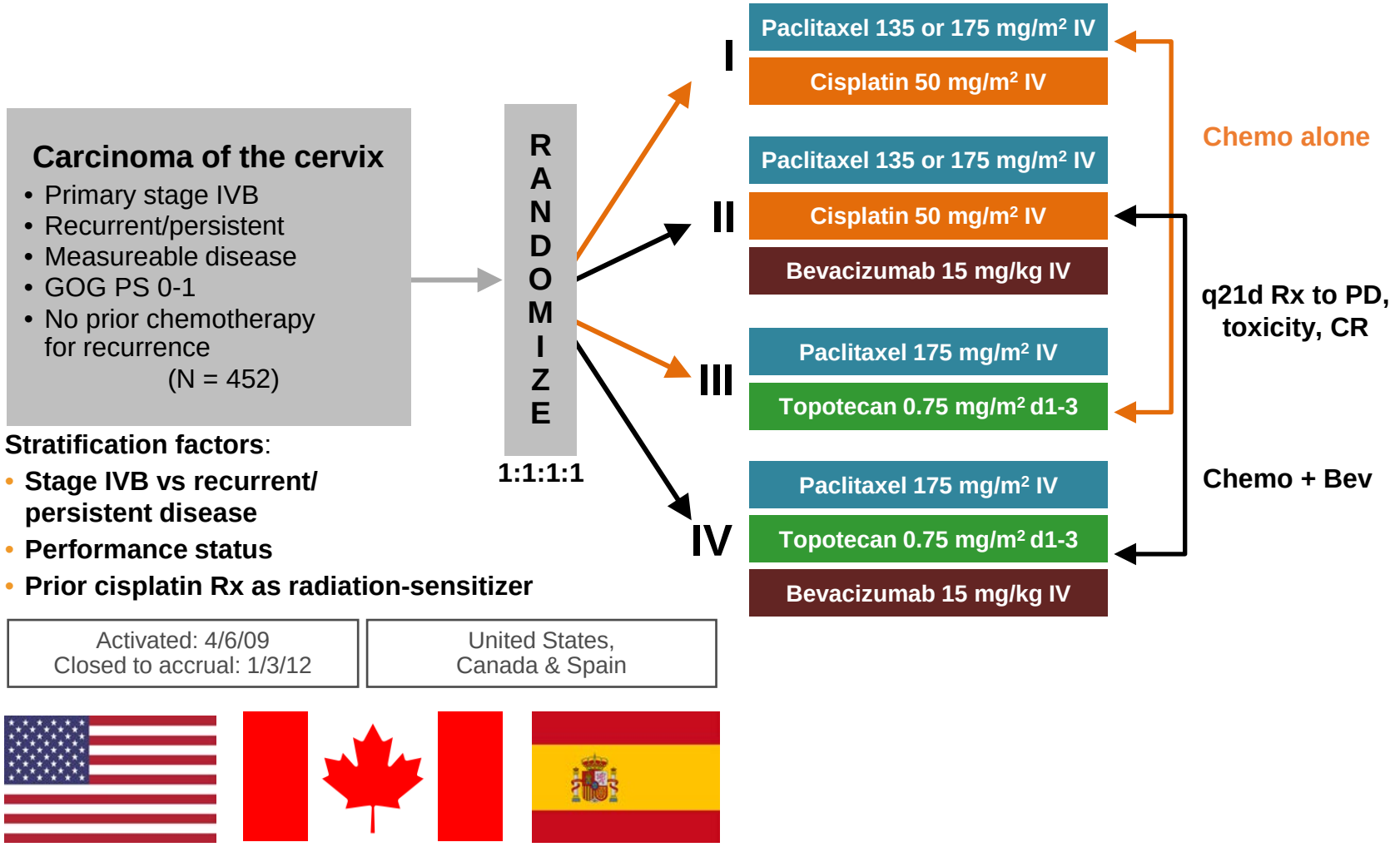
Incorporation of Bevacizumab in the Treatment of Recurrent and Metastatic Cervical Cancer

GOG 240: A Phase III 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



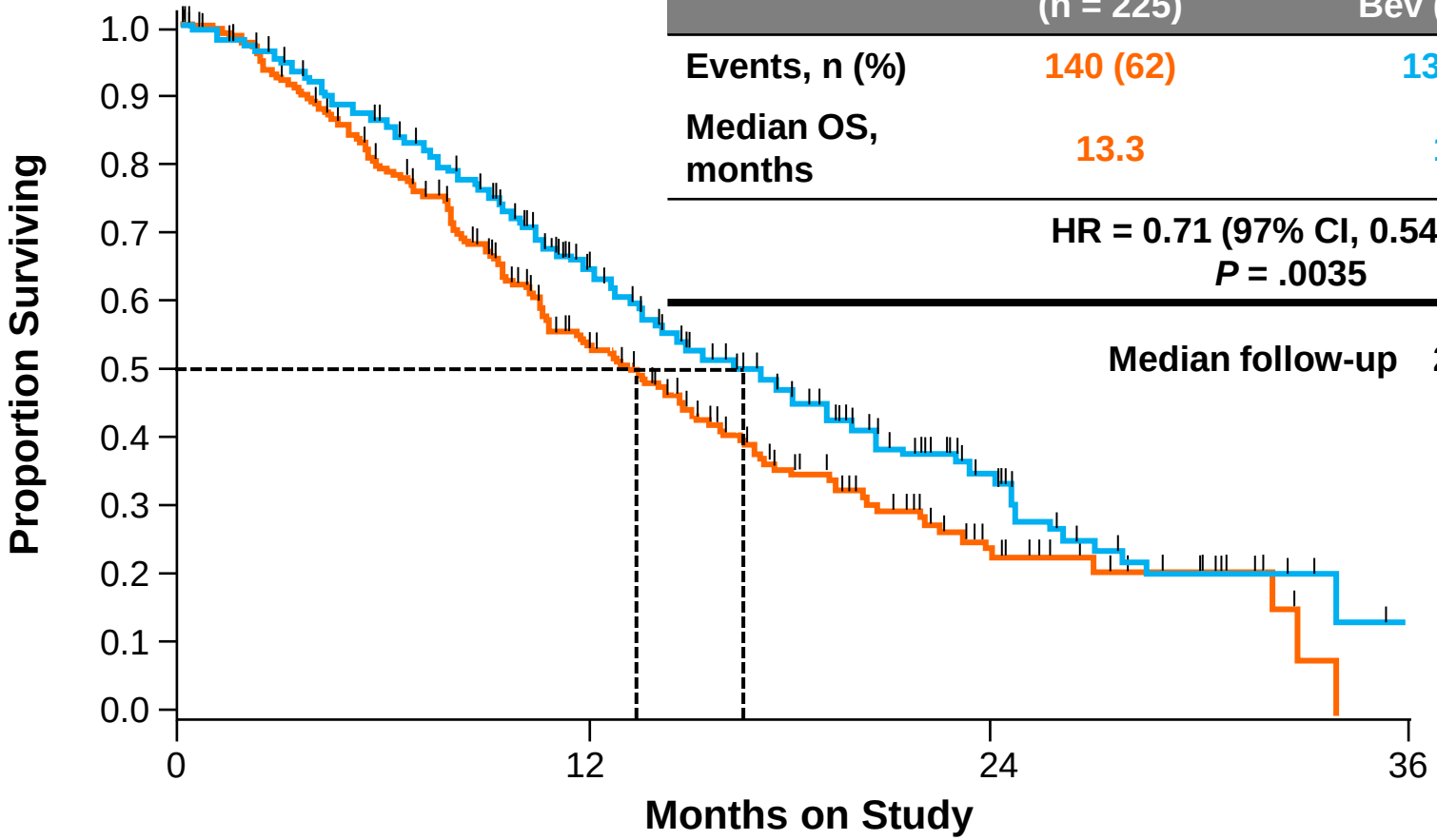
National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

GOG 240.2: 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

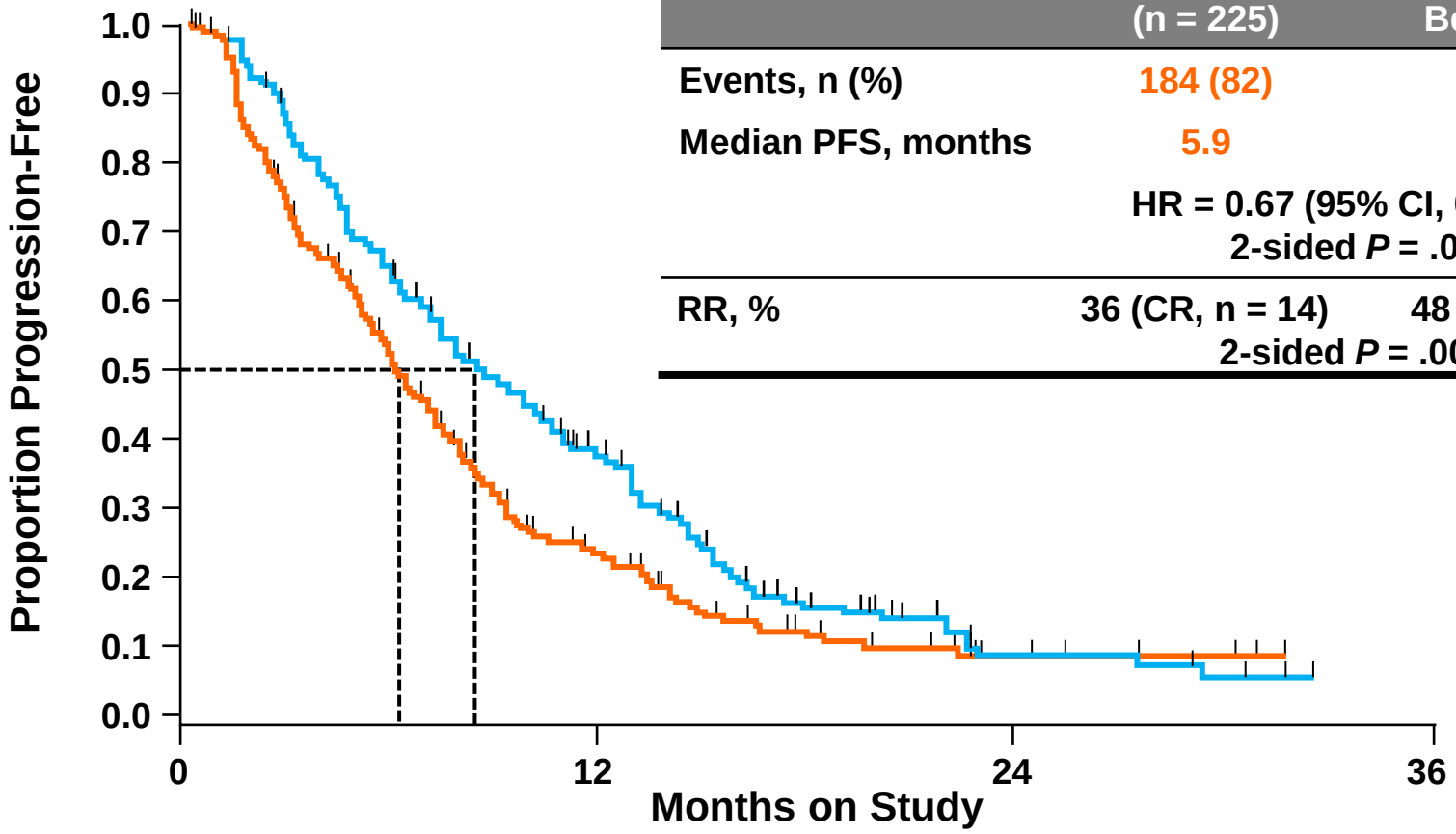
HR = 0.71 (97% CI, 0.54-0.94)
P = .0035

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.

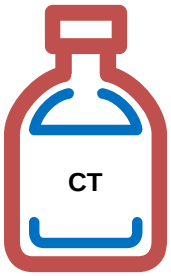
GOG 240.2: Treatment Exposure and Specific Adverse Events (AEs)

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)

*$P<.05$

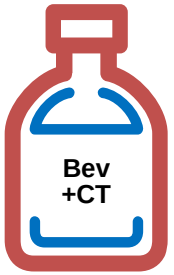
Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240: Bevacizumab Increased the Risk of Vaginal Fistulae



222 patients

GI-vaginal fistula: 2 patients (0.9%)
GU-vaginal fistula: 3 patients (1.4%)



218 patients

GI-vaginal fistula: 18 patients (8.2%)
GU-vaginal fistula: 4 patients (1.8%)
GI fistula: 1 patient (0.5%)

In a separate analysis of the GOG 240 study, all fistulae events were re-graded, and the results showed that:

- **None of the fistulae were associated with peritonitis, sepsis or death. Among the patients who developed GI-vaginal fistulae, all (100%) had received prior pelvic radiation therapy compared to 80% in the overall population.**

CT, chemotherapy; GI, gastrointestinal; GU, genitourinary

Willmott L, et al. Presented at the 15th Biennial Meeting of the International Gynecologic Cancer Society; 8-11 November, 2014: Melbourne, Australia. [abstract]

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.

CIRCCa: (Cediranib In Recurrent Cervical Cancer)

A Randomised Double Blind Phase II Trial of Carboplatin-Paclitaxel Plus Cediranib Versus Carboplatin-paclitaxel Plus Placebo in Metastatic/Recurrent Cervical Cancer

P Symonds, C Gourley, S Davidson, C West, C Dive, J Paul, K Carty, E McCartney, D Rai, S Banerjee, D Jackson, R Lord, M McCormack, E Hudson, N Reed, M Flubacher, P Jankowska, M Powell

Cedirinib—Randomized Phase II
Recurrent Cervical Cancer

Design

Randomized double-blind phase II. Patients randomized (1:1) to:-

Cediranib 20 mg daily or matched **Placebo**

in combination with Carboplatin AUC5 + Paclitaxel 175 mg/m^2 3 weekly (max 6 cycles) and then until progression/lack of tolerability

Primary Endpoint

PFS

Response Rate

	CR	PR	Overall (80% CI)
Cediranib	3 (9.4%)	18 (56.3%)	66% (53% to 77%)
Placebo	0 (0.0%)	13 (41.9%)	42% (30% to 55%)

P (1-sided) - .030

Median change in log_{10} VEGRF-2 from baseline at 28 days

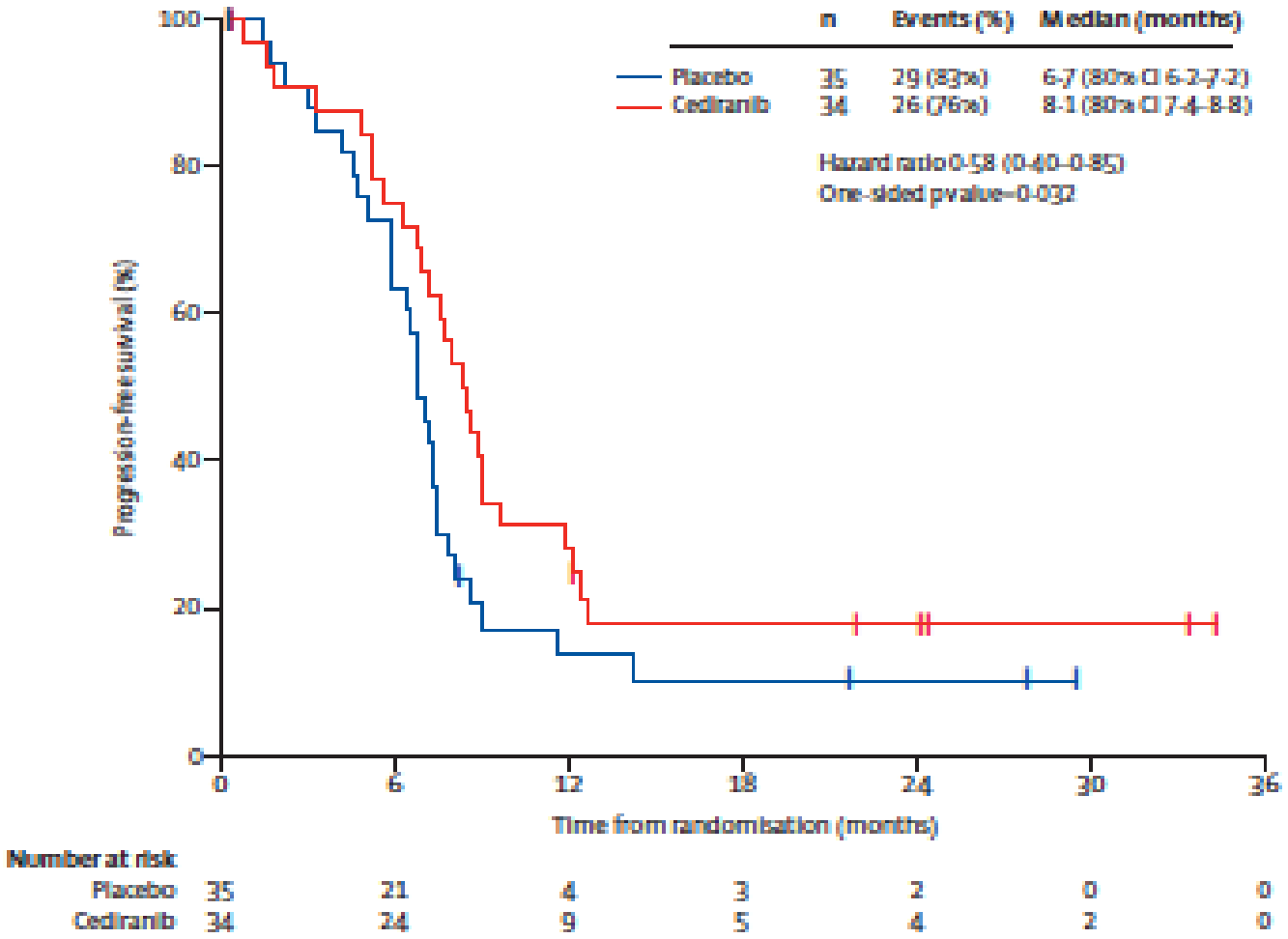
Cediranib	-0.036	(iqr* -.097 to .048, n = 18)
Placebo	0.067	(iqr* .016 to .134, n = 22)

*interquartile range

P (1-sided) <.001

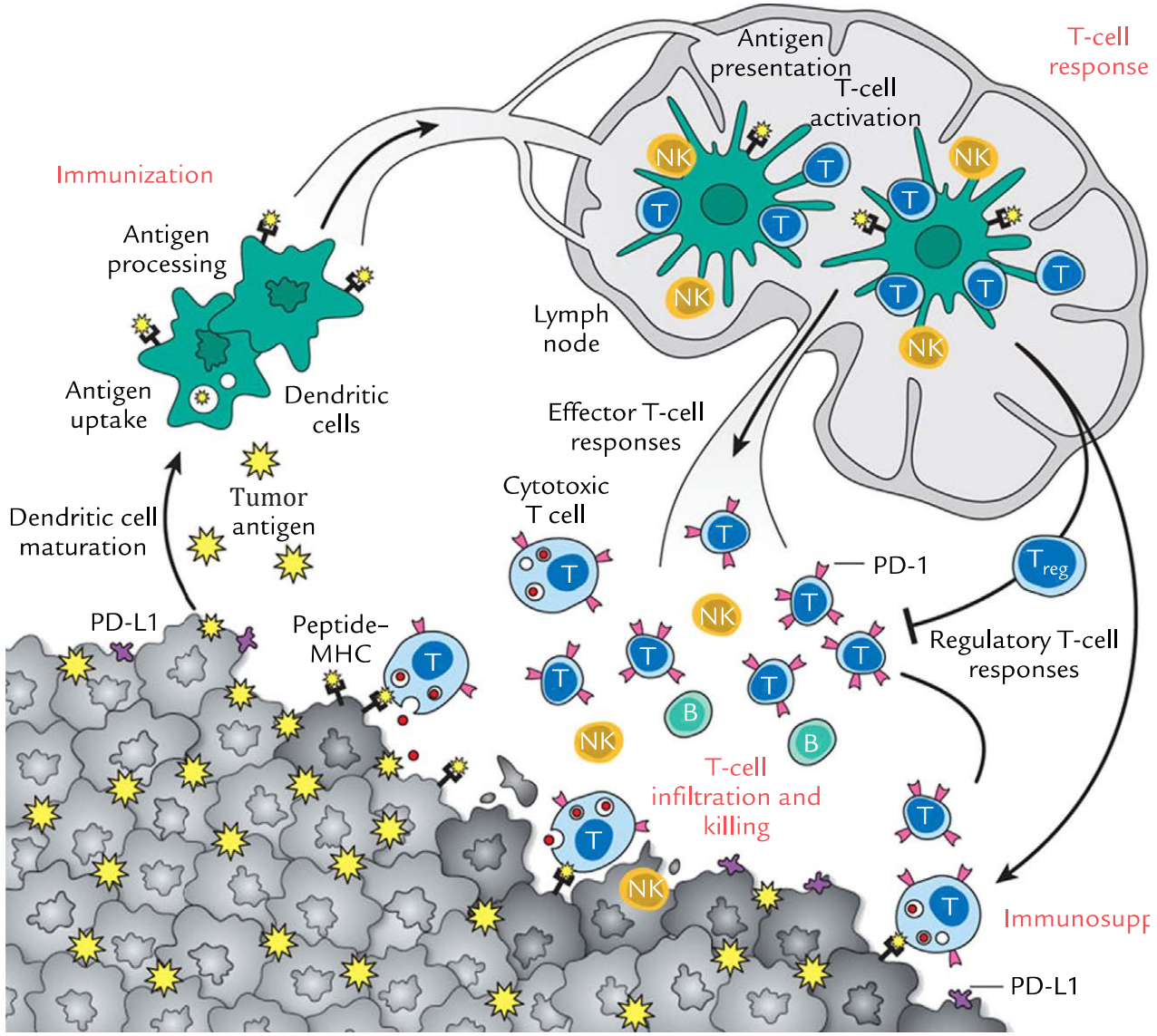
Symonds RP, et al. *Lancet Oncol.* 2015;16(15):1515-1524.

Cedirinib—PFS



Symonds RP, et al. *Lancet Oncol.* 2015;16(15):1515-1524.

Immunotherapy: The Next Frontier



Eskander RN, et al. *Clin Ther*. 2015;37(1):20-38.

HPV-Targeted Tumor-Infiltrating Lymphocytes for Metastatic Cervical Cancer

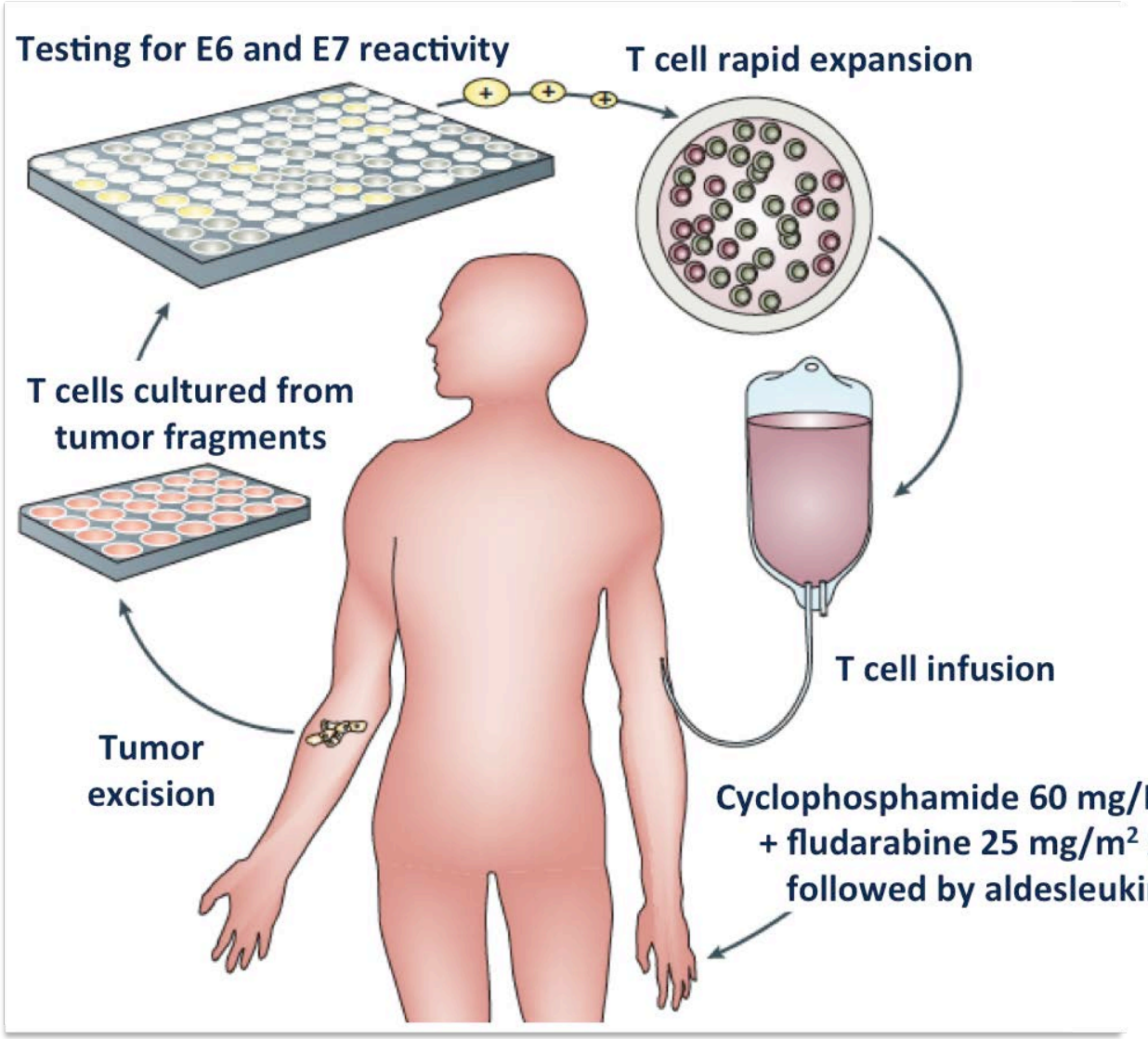
Presenting Author: Christian S. Hinrichs

Sanja Stevanović, Lindsey Draper, Robert Somerville, John Wunderlich, Nicholas P. Restifo, Richard Sherry, Giao Q. Phan, Udai S. Kammula, James C. Yang, Steven A. Rosenberg; National Cancer Institute, Bethesda, MD

Abstract LBA3008 (ASCO 2014)

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

Treatment Schema for HPV-Targeted Tumor-Infiltrating Lymphocytes (HPV-TIL)



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

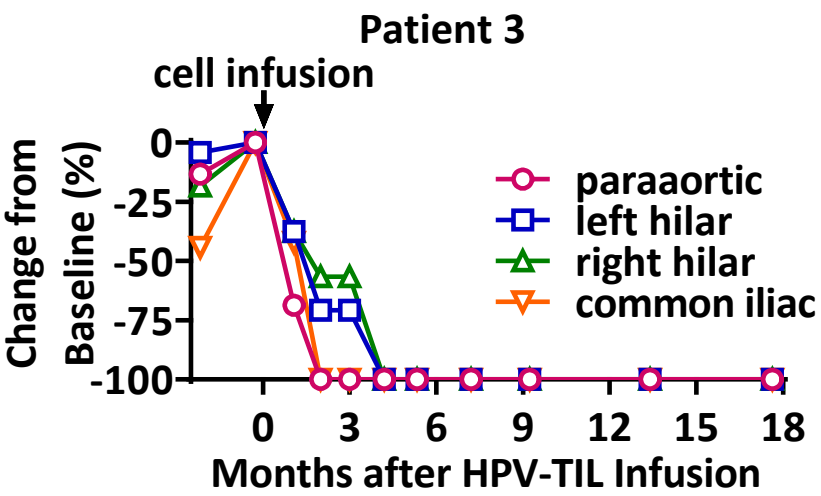
Patient Characteristics

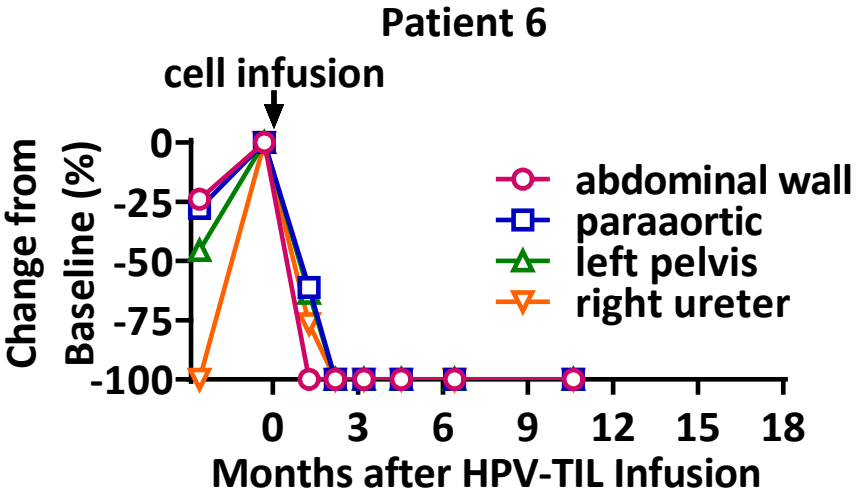
Patient	Age	Histology	HPV Type	Prior Systemic Therapy	Cell Dose ($x10^9$)	Response (Duration in Months)*
1	30	Adeno-squamous	HPV-18	Cisplatin	101	PD
2	53	Squamous	HPV-18	Cisplatin, paclitaxel, carboplatin, topotecan, ixabepilone, phase I trial	126	PR (3)
3	36	Squamous	HPV-16	Bleomycin, vincristine, cisplatin, 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.**

Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543-1550.

Prolonged Tumor Regression Following a Single Infusion of Cells

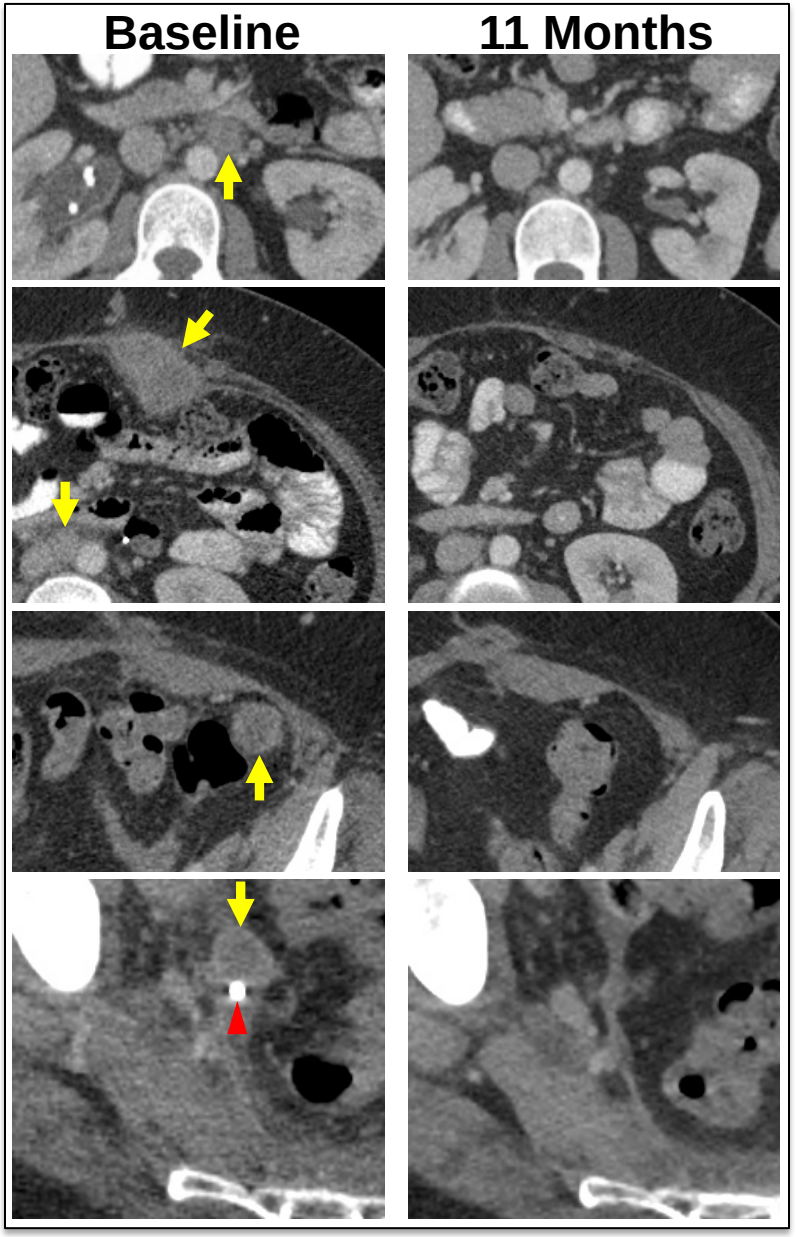




Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543-1550.

Patient 6

- 36-year-old woman
- Adenocarcinoma (HPV-18+)
- Cisplatin + radiation
- Refractory primary tumor
- Salvage surgery identified pelvic and extrapelvic progression



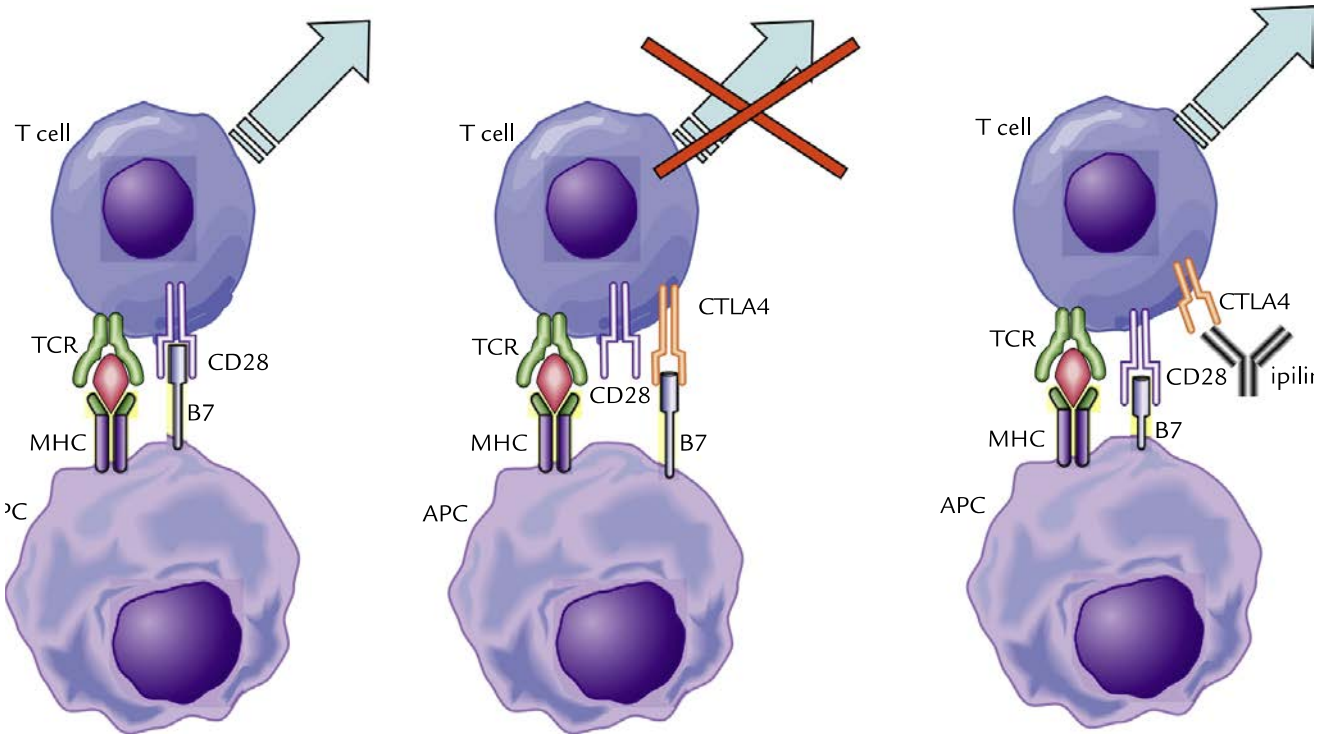
Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543-1550.

HPV-Targeted Tumor-Infiltrating Lymphocytes: Summary of the Findings

- **Objective tumor responses in 3/9 patients**
  - **1 PR (3 months), 2 CR (22+ months and 15+ months)**
- **HPV-reactive infused T cells in 6/8 patients**
  - **3/6 patients with reactivity had responses**
  - **0/2 patients without reactivity had responses**
- **Repopulation of peripheral blood with HPV reactive T cells in 2/4 patients**
  - **2/2 with repopulation had tumor responses**
  - **0/2 without repopulation had tumor responses**

Stevanovic S, et al. *J Clin Oncol.* 2015;33(14):1543-1550.

Checkpoint Inhibition: Overcoming Immune Tolerance



Lebbé C, et al. Presented at: 33rd European Society for Medical Oncology Congress; September 12-16, 2008; Stockholm, Sweden. Abstract 769O.

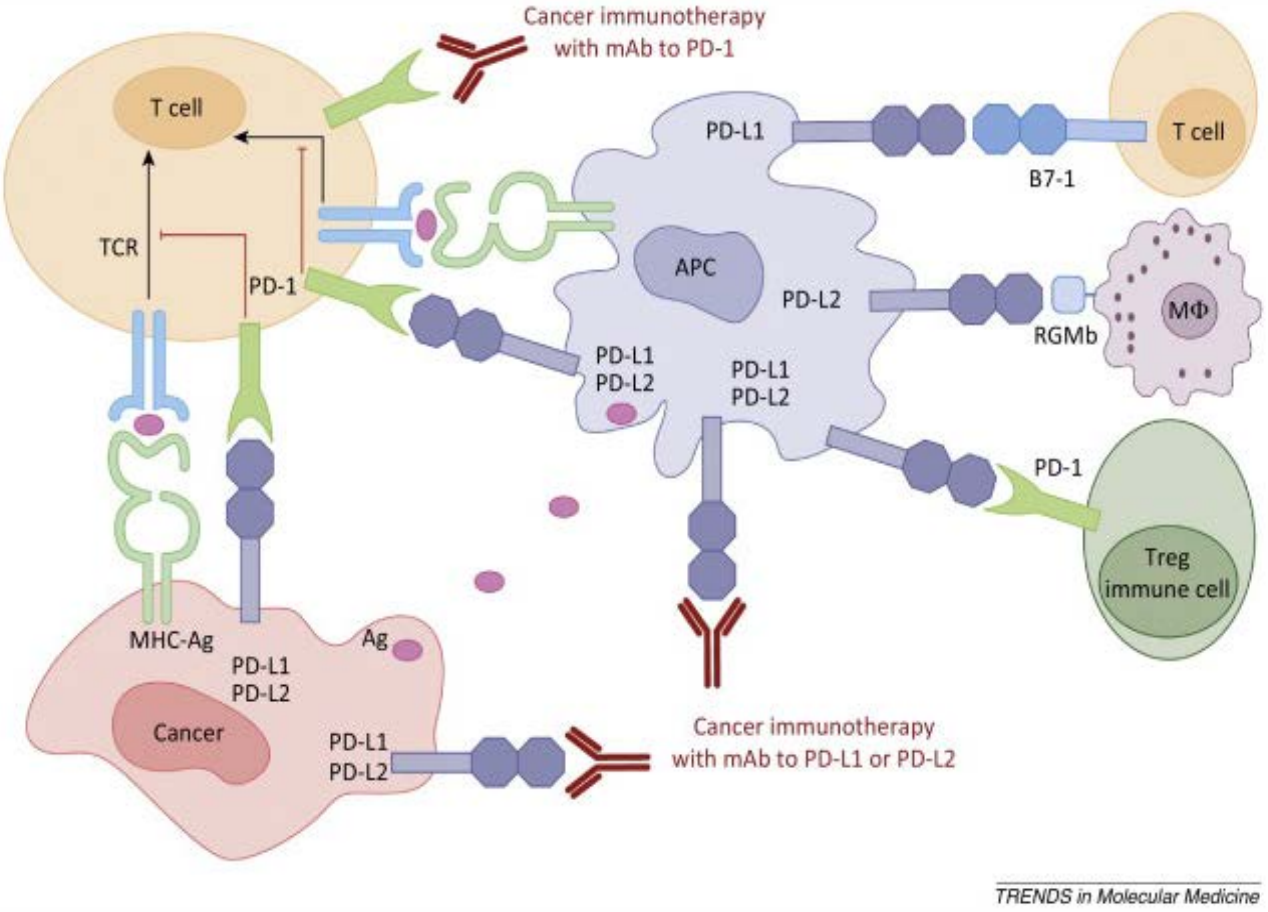
A Phase I/II Study of Ipilimumab in Metastatic or Recurrent Cervical Carcinoma

- 10 mg/kg every 21 days for four cycles; followed by four cycles of maintenance therapy (same dose) every 12 weeks
- 42 patients, median age of 49 years (23-78)
  - 29 squamous, 13 adenocarcinoma
  - 35 had prior radiation completed
  - 21 had received 2/3 prior regimens
- 34 evaluable patients: 2 PR (6%) , 9 SD and 23 PD
- Median PFS was 2.5 months (95% CI: 2.3-3.2)
- Grade 3 toxicities included diarrhea (4 patients) and colitis (3 patients)
- Did not meet the objective of 4 responders

Lheureux S, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 3061.

ClinicalTrials.gov Identifier: NCT01693783

Programmed Cell Death 1 (PD-1) and Programmed Death-Ligand 1 (PD-L1)



Longoria TC, Tewari KS. *Drugs*. 2015 Oct 16 [Epub ahead of print].

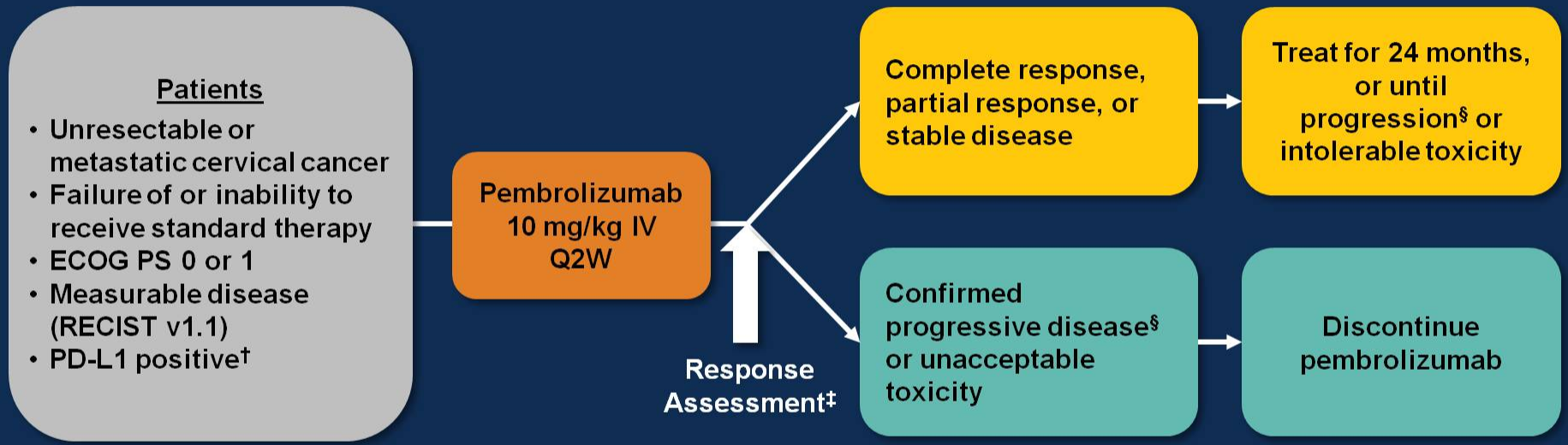
Pembrolizumab in Patients with Advanced Cervical Cancer: Preliminary Results From the Phase 1b KEYNOTE-028 Study

Jean-Sebastien Frenel,[1] Christophe Le Tourneau,[2] Bert O'Neil,[3] Patrick A. Ott,[4] Sarina Piha-Paul,[5] Carlos Gomez-Roca,[6] Emilie van Brummelen,[7] Hope Rugo,[8] Shari Thomas,[9] Sanatan Saraf,[9] Mei Chen,[9] Andrea Varga[10]

[1]Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France; [2]Institut Curie, Paris, France; [3]Indiana University Health University Hospital, Indianapolis, IN; [4]Dana-Farber Cancer Institute, Boston, MA; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Institut Claudius Regaud, Toulouse, France; [7]The Netherlands Cancer Institute, Amsterdam, Netherlands; [8]University of California, San Francisco, San Francisco, CA; [9]Merck & Co., Inc., Kenilworth, NJ; [10]Gustave Roussy, Villejuif, France

PRESENTED AT: ASCO ANNUAL MEETING '16

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors



‡Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

†Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype immunohistochemistry assay and 22C3 antibody (Merck). §Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

Baseline Characteristics

Characteristic, n (%)	N = 24
Median age, years (range)	41 (26–62)
Race, n (%)	
White	15 (63)
Asian	1 (4)
Not specified	8 (33)
ECOG performance status of 1, n (%)	18 (75)
Histology, n (%)	
Squamous cell carcinoma	23 (96)
Adenocarcinoma	1 (4)
Metastatic stage, n (%)	
MX	1 (4)
M0	6 (25)
M1	15 (63)
Unknown	2 (8)

Characteristic, n (%)	N = 24
Prior radiotherapy	23 (96)
Prior lines of therapy for advanced disease	
1	9 (38)
2	6 (25)
≥3	9 (38)
Prior platinum	23 (96)
Prior bevacizumab	10 (42)

Data cutoff date: Feb 17, 2016.

Treatment-Related Adverse Events

Any Grade Occurring in ≥2 Patients	N = 24 n (%)
Any	18 (75)
Pyrexia	4 (17)
Rash	3 (13)
Fatigue	2 (8)
Asthenia	2 (8)
Constipation	2 (8)
Diarrhea	2 (8)
Dry mouth	2 (8)
Anemia	2 (8)
Proteinuria	2 (8)
Dry skin	2 (8)
Pruritus	2 (8)

Grade 3 Occurring in ≥1 Patient	N = 24 n (%)
Any	5 (21)
Rash	2 (8)
Neutropenia	1 (4)
Colitis	1 (4)
Guillain-Barre syndrome	1 (4)
Proteinuria	1 (4)

- Median follow-up duration: 43 weeks (range, 6–92)
- No grade 4 treatment-related AEs
- No treatment-related mortality
- 2 treatment-related discontinuations: grade 3 colitis; grade 3 Guillain-Barre syndrome

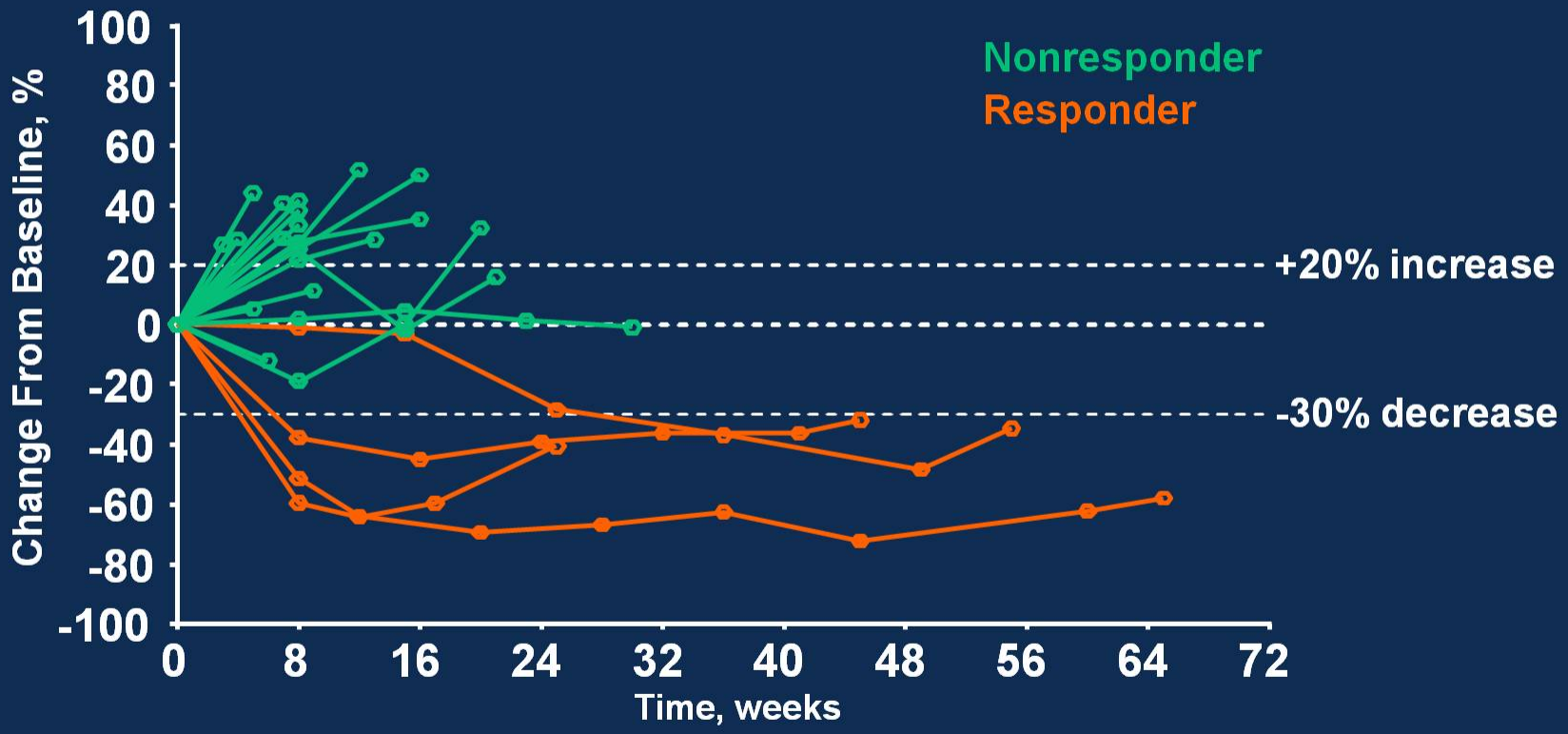
Data cutoff date: Feb 17, 2016.
Includes patients who received ≥1 dose of pembrolizumab.

Antitumor Activity (RECIST v1.1, Investigator Review)

	N = 24		
	n	%	95% CI
ORR†	4	17	5–37
Partial response	4	17	5–37
Stable disease	3	13	3–32
Progressive disease	16	67	45–84
No assessment‡	1	4	<1–21

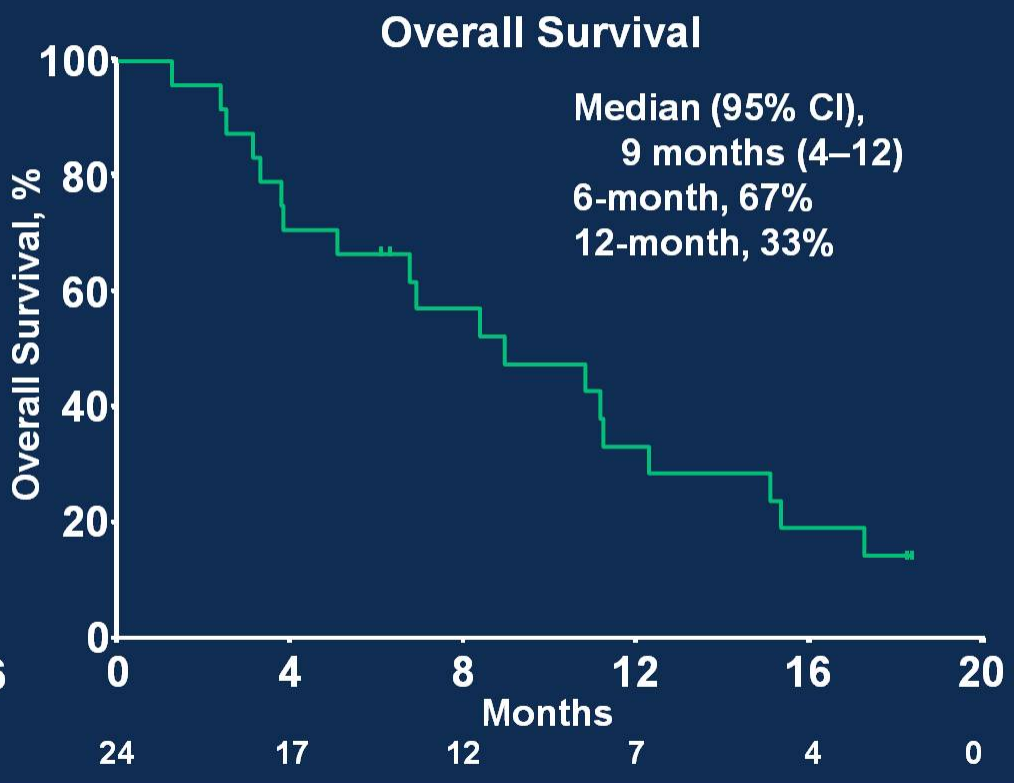
Data cutoff date: Feb 17, 2016. Only confirmed responses are included. Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included.
†There were no complete responses. ‡Patient did not have a postbaseline response evaluation.

Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Investigator Review)



Data cutoff date: Feb 17, 2016. Patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a post-baseline assessment are included (n = 20). One patient was excluded due to 2 scans for the same assessment out of window.

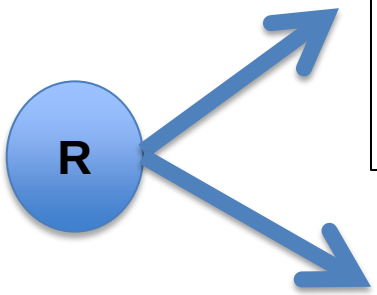
Progression-Free Survival† and Overall Survival



Data cutoff date: Feb 17, 2016.
Patients who received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease per RECIST v1.1 are included. †RECIST v1.1 by investigator review.

AN OPEN-LABEL, RANDOMIZED, PHASE 3 CLINICAL TRIAL OF REGN2810* VERSUS PHYSICIANS CHOICE CHEMOTHERAPY (PCC)

- Recurrent squamous or adenocarcinoma of the cervix
- Measurable disease by RECIST 1.1
- Tumor progression or recurrence within 6 months of last dose of platinum therapy used to treat metastatic, persistent or recurrent cancer



PCC:
Pemetrexed
Topetecan or Ironotecan
Vinorelbine
until progression

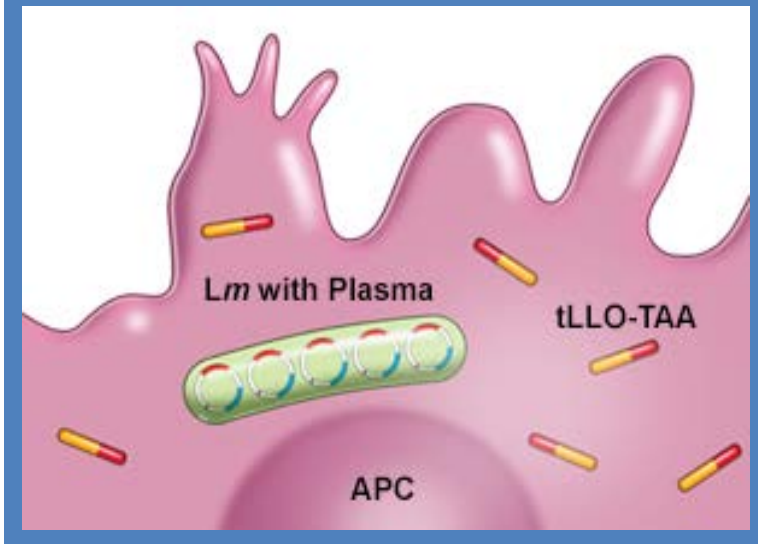
REGN2810:
IV 350 mg q3w for 48 weeks or until progression

Primary endpoint: OS
Secondary endpoints: PFS, Overall Response Rate, Adverse events, Quality of life
Statistics: Sample size = 414, 1-sided alpha = 0.025, 90% power, target HR = 0.7, stratification factors (region, PCC, histology)

*REGN2810 is a high affinity hinge-stabilized IgG4^{P} human antibody to the PD-1 receptor that blocks PD-1/PD L1-mediated T cell inhibition

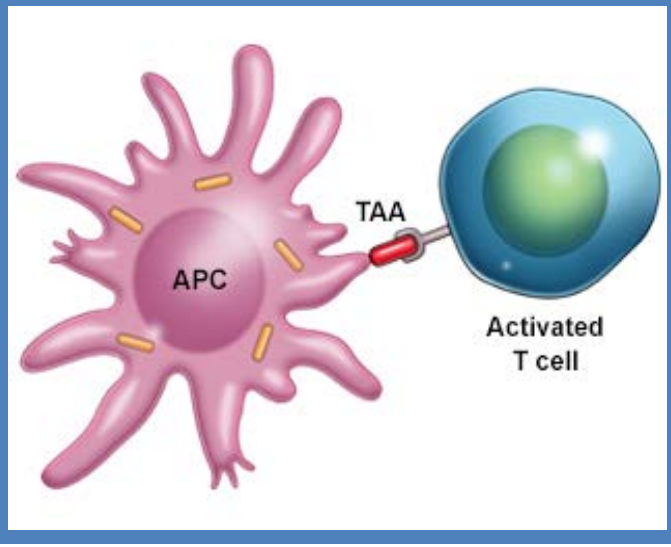
Listeria as an Antigen Vector

_Lm_ Technology stimulates a tumor-targeted immune response directed by plasmids



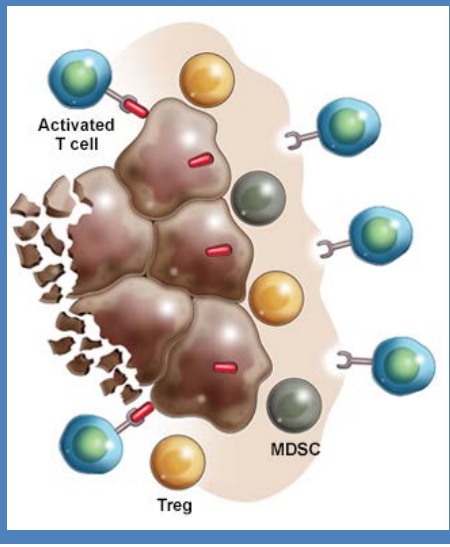
Attenuated *Lm* trigger a robust immune response and bioengineered plasmids generate a fusion protein, tLLO-TAA

...so that cancer can be recognized



TAA activates cytotoxic T-cells targeted against the tumor

...and killed

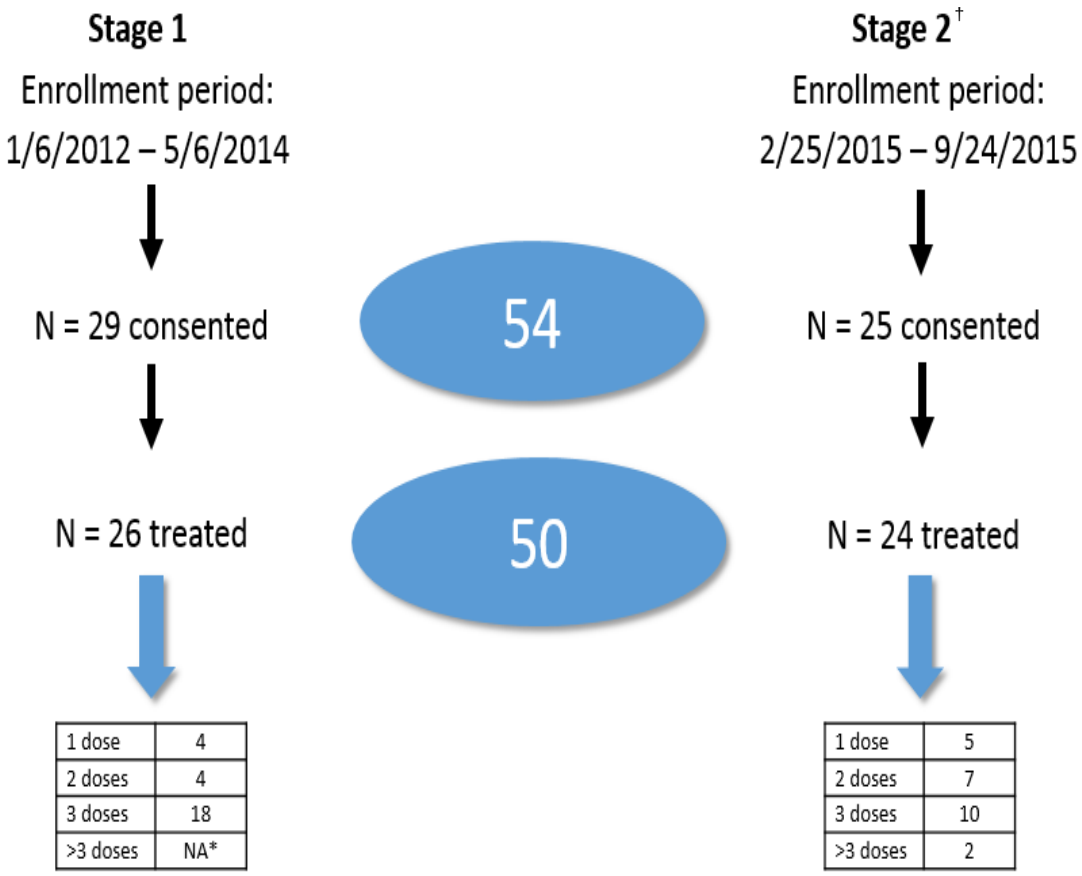


T-cells target TAA on tumor cells and tLLO inhibitsTreg and MDSC in the TME, reducing the tumor's protective shield

Source: Advaxis; used with permission

APC, antigen presenting cell; *Lm*, *Listeria monocytogenes*; MHC, major histocompatibility complex; TCR, T-cell receptor; MDSC, myeloid-derived suppressor cells; TAA, tumor-associated antigen; tLLO, truncated listeriolysin O; Treg, regulatory T cell; TME, tumor microenvironment

GOG/NRG-0265: CONSORT diagram



Stage 1 completed; Stage 2 enrollment initiated

†In October 2015 all trials of AXAL were placed on a brief clinical hold by the US Food and Drug Administration, for investigation of an isolated safety concern; the hold was subsequently lifted in Dec 2015.
*Maximum 3 doses allowed by protocol.
AXAL, axalimogene filolisbac; NA, not applicable.

Huh W et al SGO 2017

Treatment-emergent adverse event summary

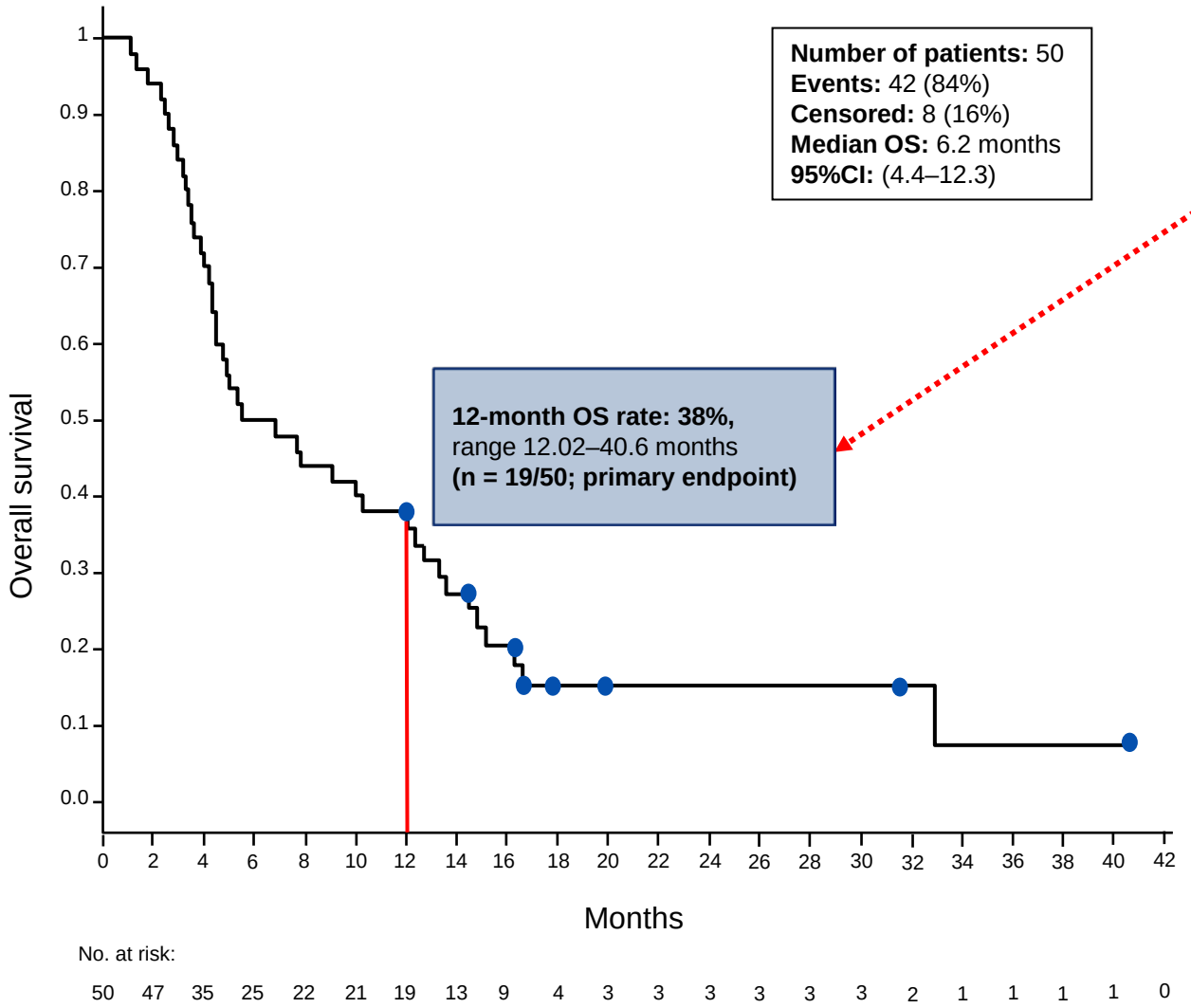
- All treated patients (N = 50) experienced ≥1 AE; safety findings from both stages of the study were consistent

AE	Grade 1–4	Grade 1–2	Grade 3	Grade 4
Patients with ≥1 TRAE, n (%)	48 (96)	28 (56)	18 (36)	2 (4)*
TRAEs occurring in ≥30% of patients				
Fatigue	26 (52)	26 (52)	-	-
Chills	26 (52)	26 (52)	-	-
Anemia	24 (48)	19 (38)	5 (10)	-
Nausea	16 (32)	16 (32)	-	-
Fever	15 (30)	15 (30)	-	-

*The observed grade 4 TRAEs recorded in 2 patients were considered *possibly related* (lung infection [klebsiella related] and sepsis; same patient) or *probably related* (hypotension and cytokine related symptoms; same patient) to treatment.
AE, adverse event; TRAE; treatment-related AE.

Huh W et al SGO 2017

12-month and median overall survival



- Represents a 52% improvement vs logistic model-predicted milestone survival rate of 24.5%
- The probability of this survival advantage being detected by chance vs a true treatment effect was 0.02
- 8 patients remain alive as of January 31, 2017

CI, confidence interval; OS, overall survival.

Huh W et al SGO 2017

Objective response rates

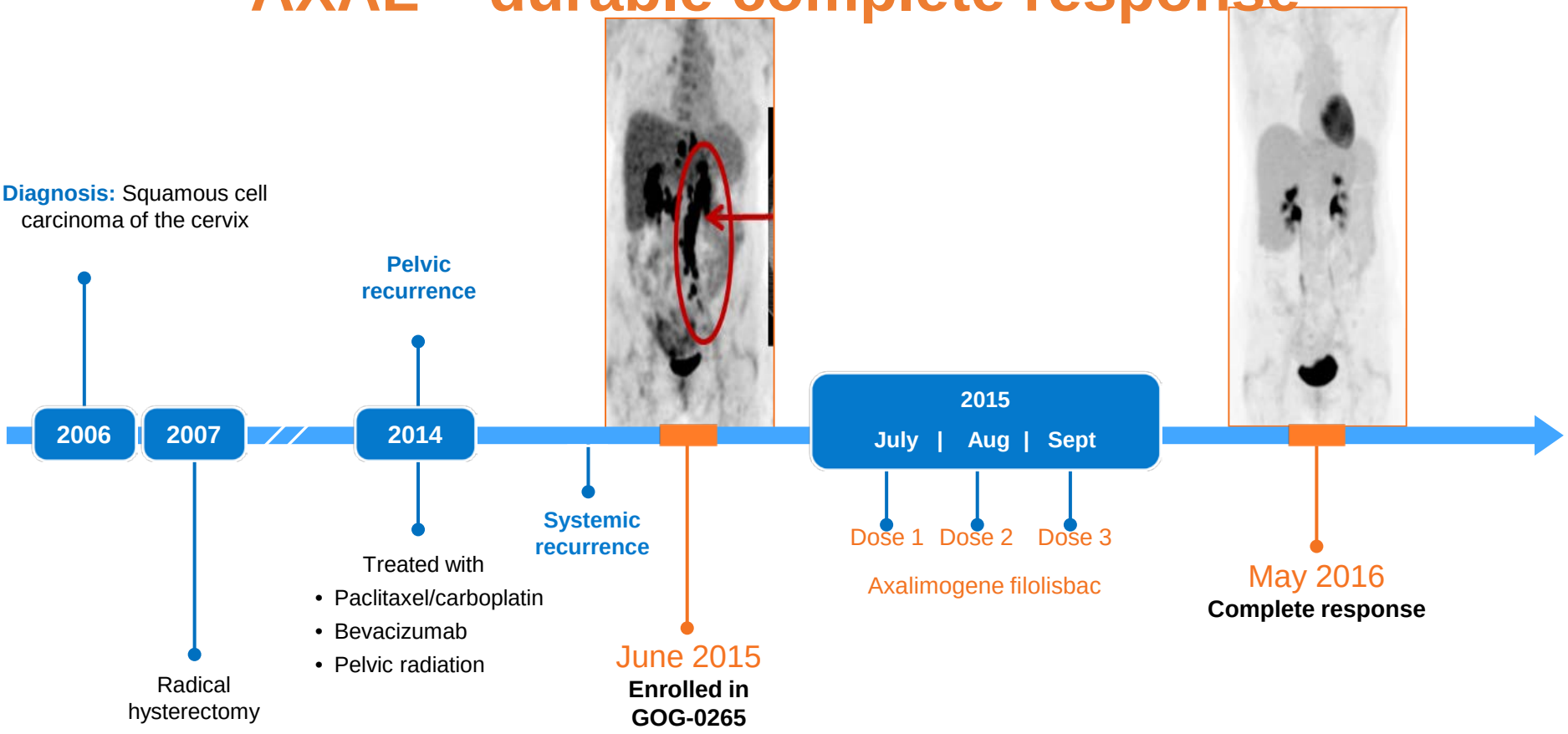
- Investigator assessment of tumor best response was reported in 38 patients (76%)

Tumor Best Response	Overall (N = 50)
CR	1 (2)
SD	15 (30)
PD	22 (44)
NE	10 (20)
Missing post-baseline scan	2 (4)

Note: These are unconfirmed.
CR, complete response; NE, no evaluation; OR, objective response; PD, progressive disease; SD, stable disease.

Huh W et al SGO 2017

Study GOG-0265: 66-year-old patient treated with AXAL – durable complete response



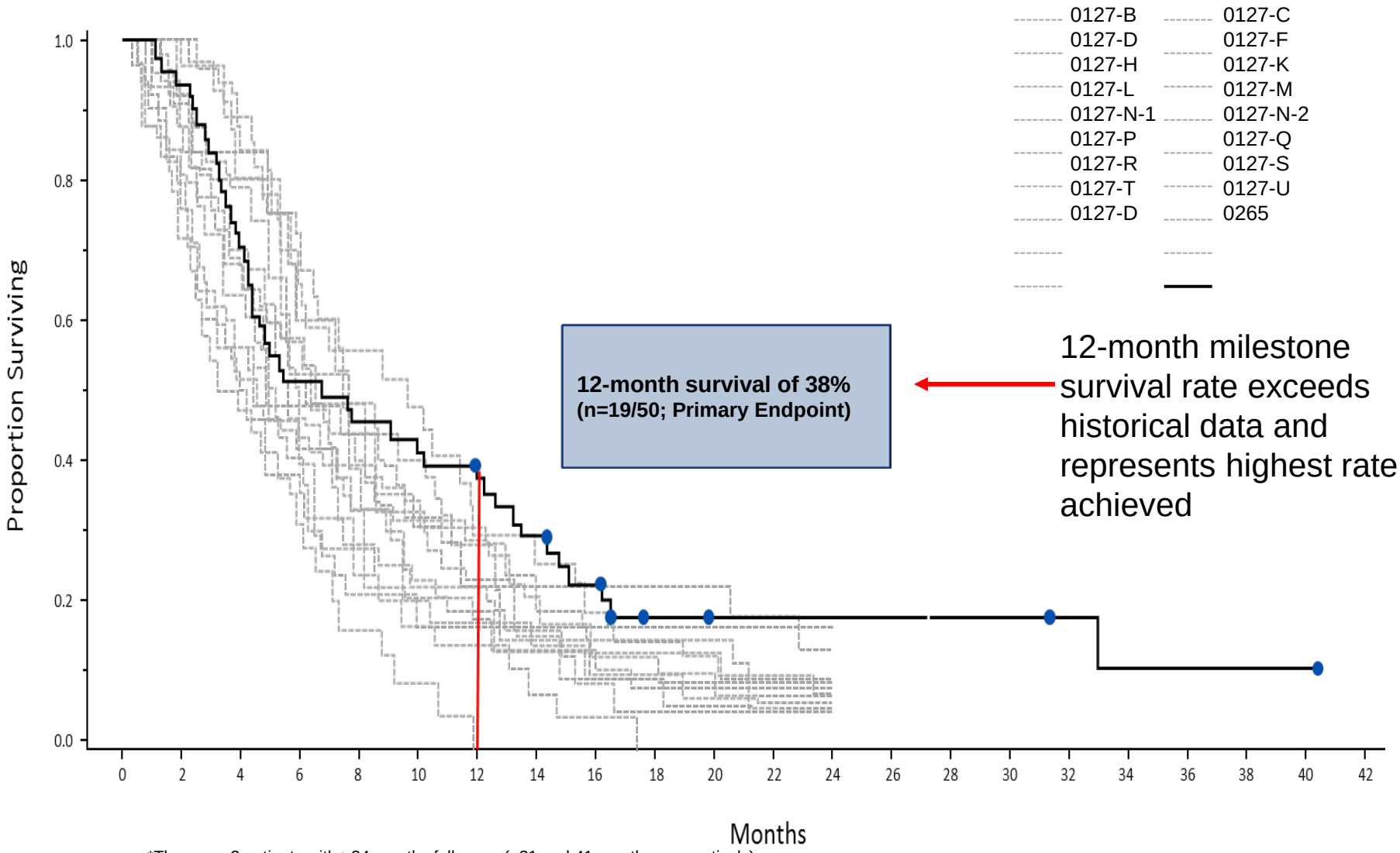
Survival *to date* – second-line metastatic squamous cell cervical carcinoma (post-bevacizumab): 18.5 months*

TRAEs: Grade 1–2 fatigue, chills, fever, nausea, and grade 3 hypotension, cytokine release syndrome; no grade 4–5 TRAEs reported

AXAL, axalimogene filolisbac; TRAE, treatment-related adverse event.
*Calculated from date of first AXAL dose (July 16, 2015) to data cut-off (Jan 31, 2017)
Results may not be typical; further study is warranted.

Huh W et al SGO 2017

GOG/NRG-0265 Survival in the Context of Historical GOG Trials in Second-line

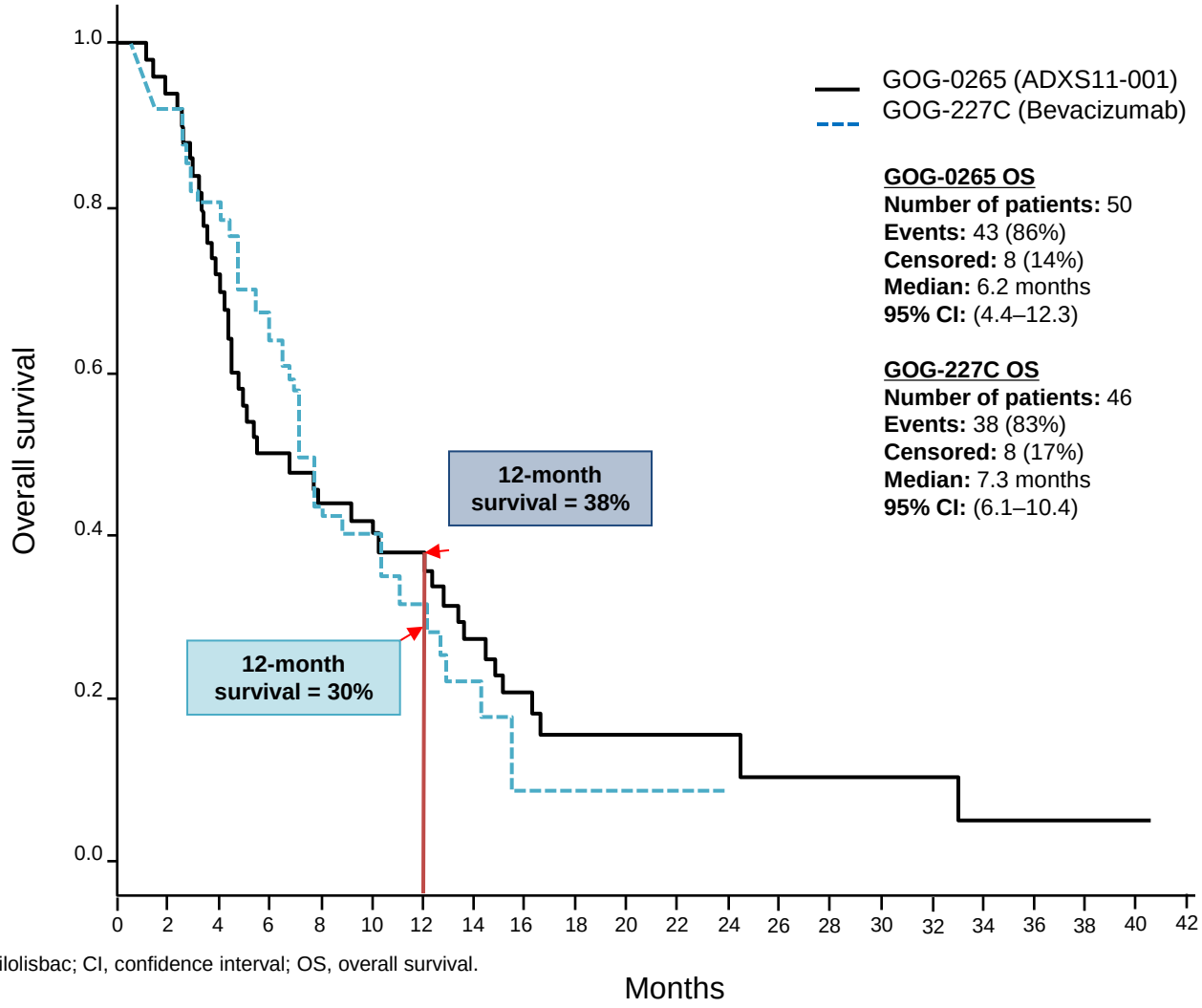


12-month milestone survival rate exceeds historical data and represents highest rate achieved

*There are 2 patients with >24 months follow up (~31 and 41 months, respectively).
GOG, Gynecologic Oncology Group; OS, overall survival; PRmCC, persistent/recurrent metastatic cervical cancer.

Huh W et al SGO 2017

AXAL GOG/NRG-0265 and bevacizumab GOG-227C: 12-month overall survival curves



AXAL, axalimogene filolisbac; CI, confidence interval; OS, overall survival.

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

Next steps: Phase 3 AIM2CERV studies – AXAL as adjuvant monotherapy to prevent recurrence in high-risk cervical cancer

- HRLACC
- FIGO stage I–II with positive pelvic nodes
- FIGO stage III–IVA
- Any FIGO stage with para-aortic nodes

Treatment with cisplatin (at least 4-wk exposure) and radiation (minimum 40-Gy external beam radiation therapy)

Randomize

Placebo IV
Up to 1 year
N = 150

Axalimogene filolisbac
(1 × 10^9 CFU)
Up to 1 year
N = 300

Primary endpoint:

DFS

Baseline tumor imaging must be performed within 28 days before the first study treatment infusion

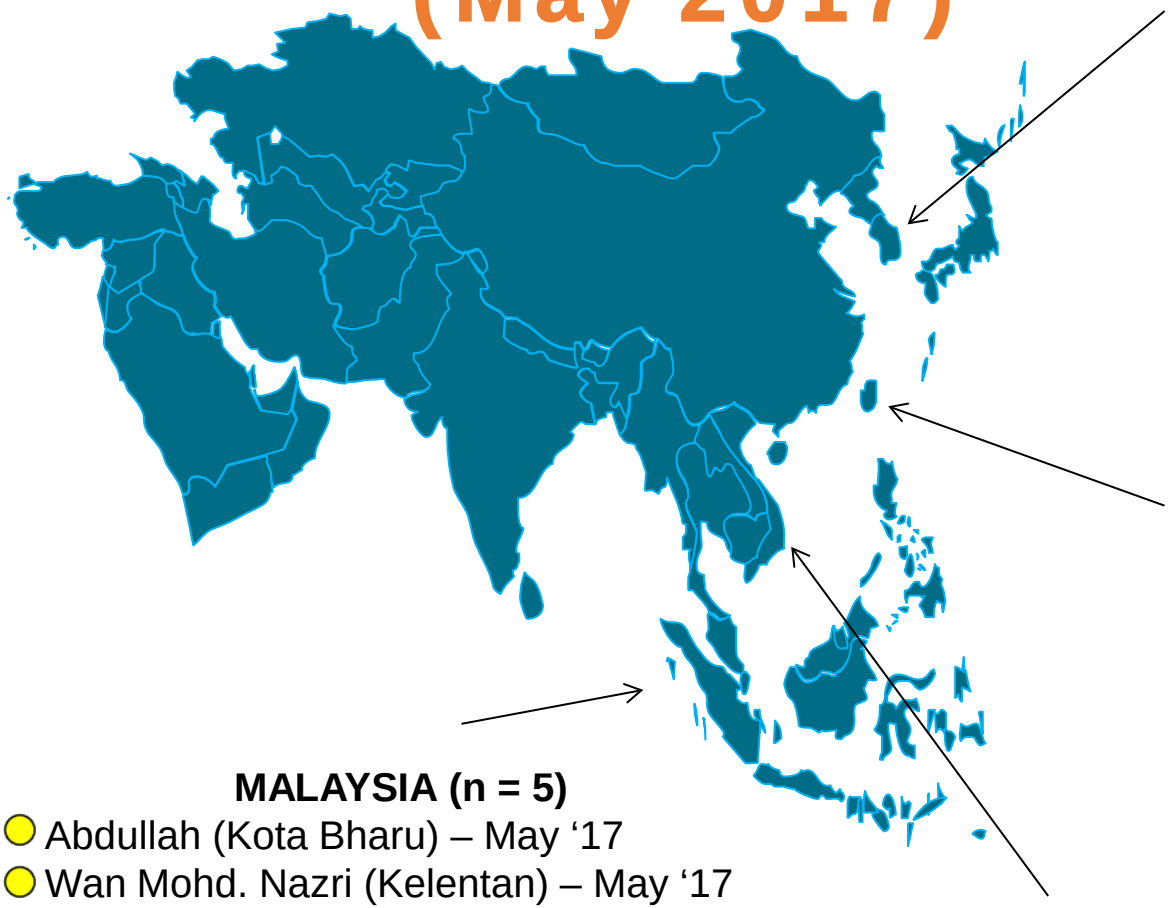
ClinicalTrials.gov Identifier: NCT02853604

AIM2CERV – Axalimogene Filolisbac Immunotherapy Following Chemo/Radiation in Patients Who Have High-Risk Locally Advanced Cervical Cancer (HRLACC)

CFU, colony-forming unit; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics; HRLACC, high-risk locally advanced cervical cancer; IV, intravenous.

1. Herzog T, et al. SITC 2016. Poster 145.

AIM2CERV Sites – Asia Map (May 2017)



SOUTH KOREA (n = 8)

- Choi (Seoul) – June ‘17
- Kim Gun Min (Seoul) – June ‘17
- Kim Byong-Gie (Seoul) – June ‘17
- Kim Jae-Hoon (Seoul) – June ‘17
- Moon (Seongnam) – Aug ‘17
- Nam (Seoul) – June ‘17
- Ryu (Seoul) – June ‘17
- Song (Gyeongsangnam) – June ‘17

TAIWAN (n = 6)

- Cheng Wen-Fang (Taipei)
- Chung, Chi-Feng (Taipei)
- Ho (Taipei)
- Lu (Taichung)
- Chang (Taoyuan) – May ‘17
- Chou (Tainan)

MALAYSIA (n = 5)

- Abdullah (Kota Bharu) – May ‘17
- Wan Mohd. Nazri (Kelentan) – May ‘17
- Yong Chee Ming (Ampang) – May ‘17
- Mat Adenan (Kuala Lumpur) – May ‘17
- Appalanaido (Pulau Pinang) – May ‘17

VIETNAM (n = 1)

- Linh (Ho Chi Minh City) – Nov ‘17

LEGEND

- Open site (n = 5)
- Opening pending (n = 15)

*** Site selection in China pending**

Summary and Conclusions

- **Antiangiogenesis was the first validated targeted intervention in cervical cancer**
- **Immunotherapy is the next frontier**
  - **Checkpoint inhibitors (PD-1, PDL-1, CTLA4)**
  - **Listeria-based vectors**

Thank You

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