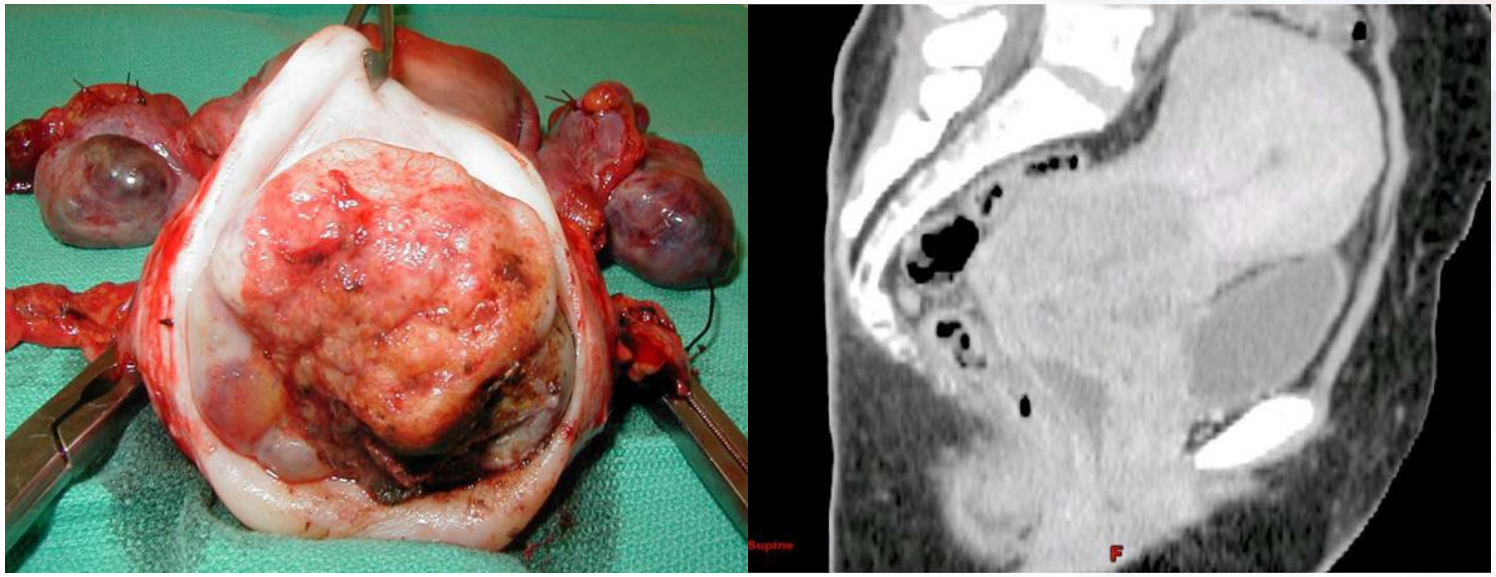
Cervical Cancer



R. Wendel Naumann, MD

Levine Cancer, Atrium Heath/Wake Forest University

Financial Disclosures

Consulting or Advisory Role
Company: Merck Sharp & Dohme
Company: AstraZeneca
Company: Eisai
Company: Bristol-Myers Squibb
Company: Seagen
Company: Agenus
Company: SturoBio
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Company: Genelux
Company: Laekna
Company: Immunogen
Company: EMD Serono
Company: Johnson&Johnson

DSMB
Company: Intuitive (GOG 3043)
Company: GeneLux (GOG 3076)

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Learning Objectives

- Become familiar with the progress made in preventing and treating cervical cancer

-Understand new developments in the treatment of cervical cancer

Gynecologic Cancers - 1.33 million cases

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)		NO. OF NEW DEATHS (% OF ALL SITES)	
Female breast	2,261,419	(11.7)	684,996	(6.9)
Lung	2,206,771	(11.4)	1,796,144	(18.0)
Prostate	1,414,259	(7.3)	375,304	(3.8)
Nonmelanoma of skin [a]	1,198,073	(6.2)	63,731	(0.6)
Colon	1,148,515	(6.0)	576,858	(5.8)
Stomach	1,089,103	(5.6)	768,793	(7.7)
Liver	905,677	(4.7)	830,180	(8.3)
Rectum	732,210	(3.8)	339,022	(3.4)
Cervix uteri	604,127	(3.1)	341,831	(3.4)
Esophagus	604,100	(3.1)	544,076	(5.5)
Thyroid	586,202	(3.0)	43,646	(0.4)
Bladder	573,278	(3.0)	212,536	(2.1)
Non-Hodgkin lymphoma	544,352	(2.8)	259,793	(2.6)
Pancreas	495,773	(2.6)	466,003	(4.7)
Leukemia	474,519	(2.5)	311,594	(3.1)

[a] New cases exclude basal cell carcinoma, whereas deaths include all types of nonmelanoma skin cancer.

Source: GLOBOCAN 2020.

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)		NO. OF NEW DEATHS (% OF ALL SITES)	
Non-Hodgkin lymphoma	544,352	(2.8)	259,793	(2.6)
Pancreas	495,773	(2.6)	466,003	(4.7)
Leukemia	474,519	(2.5)	311,594	(3.1)
Kidney	431,288	(2.2)	179,368	(1.8)
Corpus uteri	417,367	(2.2)	97,370	(1.0)
Lip, oral cavity	377,713	(2.0)	177,757	(1.8)
Melanoma of skin	324,635	(1.7)	57,043	(0.6)
Ovary	313,959	(1.6)	207,252	(2.1)
Brain, nervous system	308,102	(1.6)	251,329	(2.5)
Larynx	184,615	(1.0)	99,840	(1.0)
Multiple myeloma	176,404	(0.9)	117,077	(1.2)
Nasopharynx	133,354	(0.7)	80,008	(0.8)
Gallbladder	115,949	(0.6)	84,695	(0.9)
Oropharynx	98,412	(0.5)	48,143	(0.5)
Hypopharynx	84,254	(0.4)	38,599	(0.4)

[a] New cases exclude basal cell carcinoma, whereas deaths include all types of nonmelanoma skin cancer.

Sung H, CA CANCER J CLIN 2021;71:209–249

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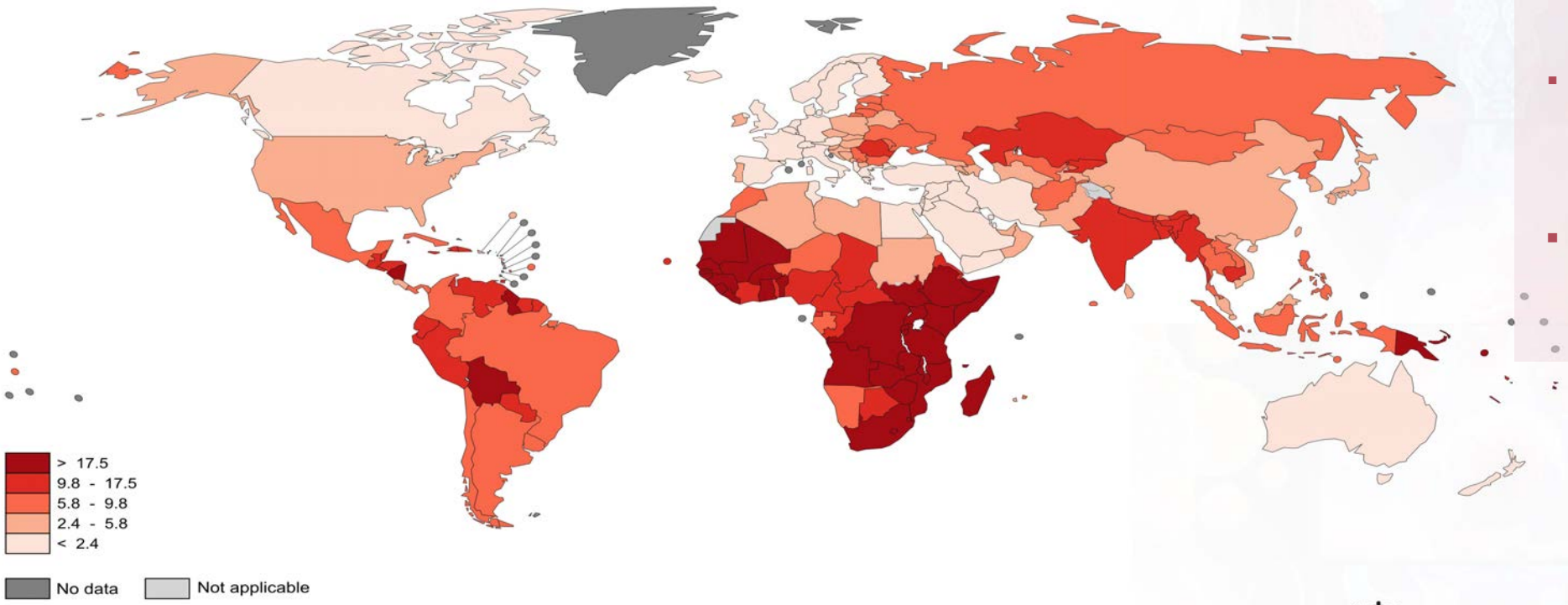
GLOBAL BURDEN OF CERVCIAL CANCER



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

- **4th** most common cancer among women
- Incidence: estimated **570,000** new cases globally in 2018
- **90%** of deaths in low- and middle-income countries

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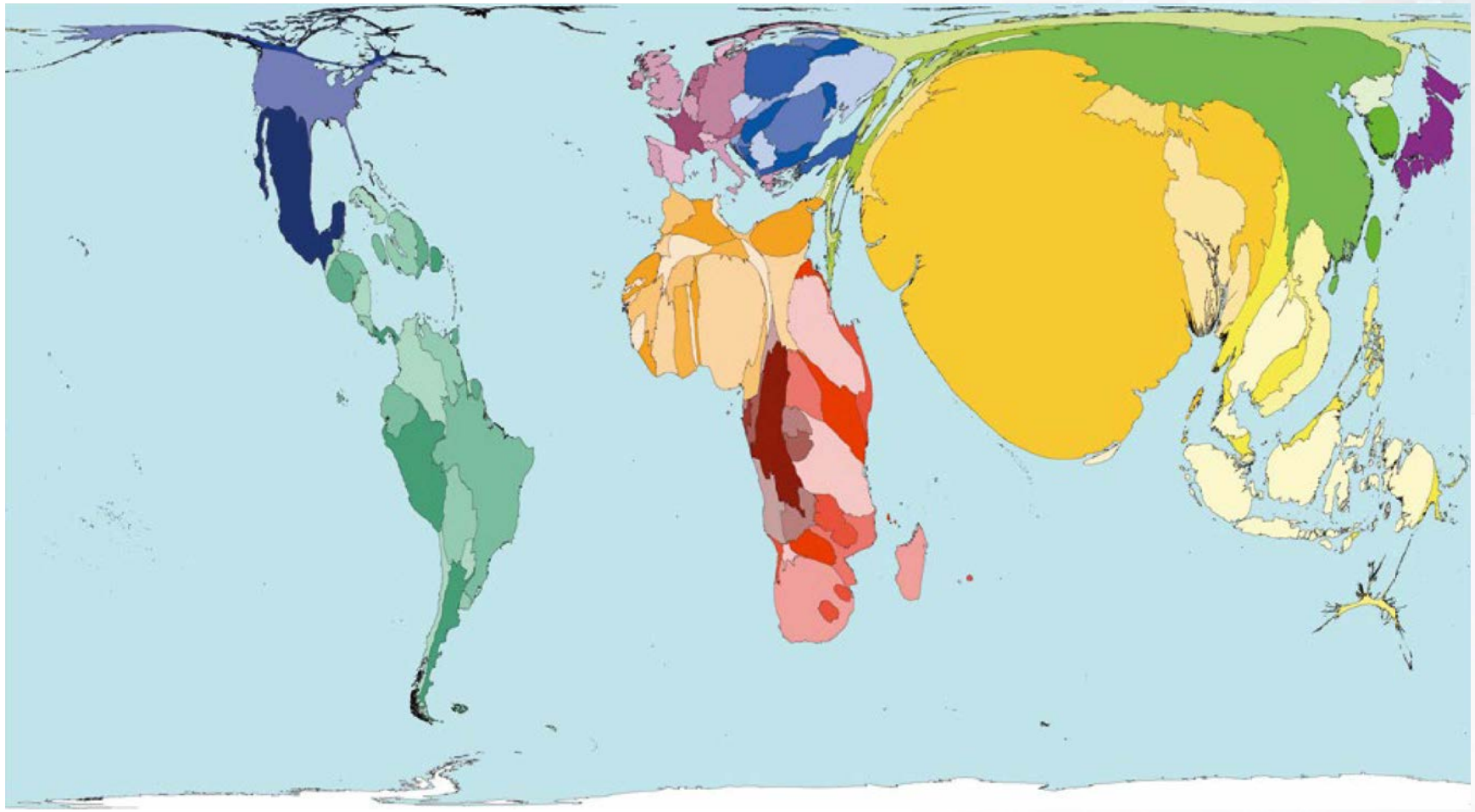
World Mapper Cervical Cancer Deaths



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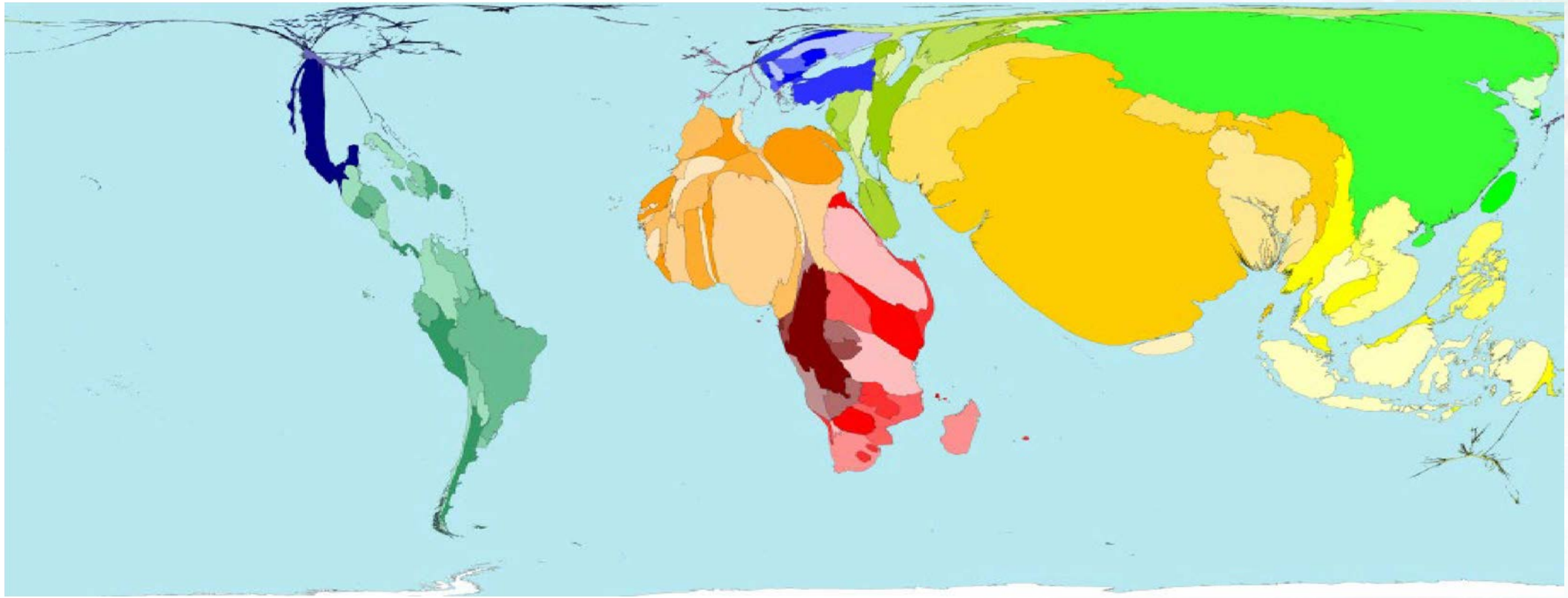
People Living on <$10/Day



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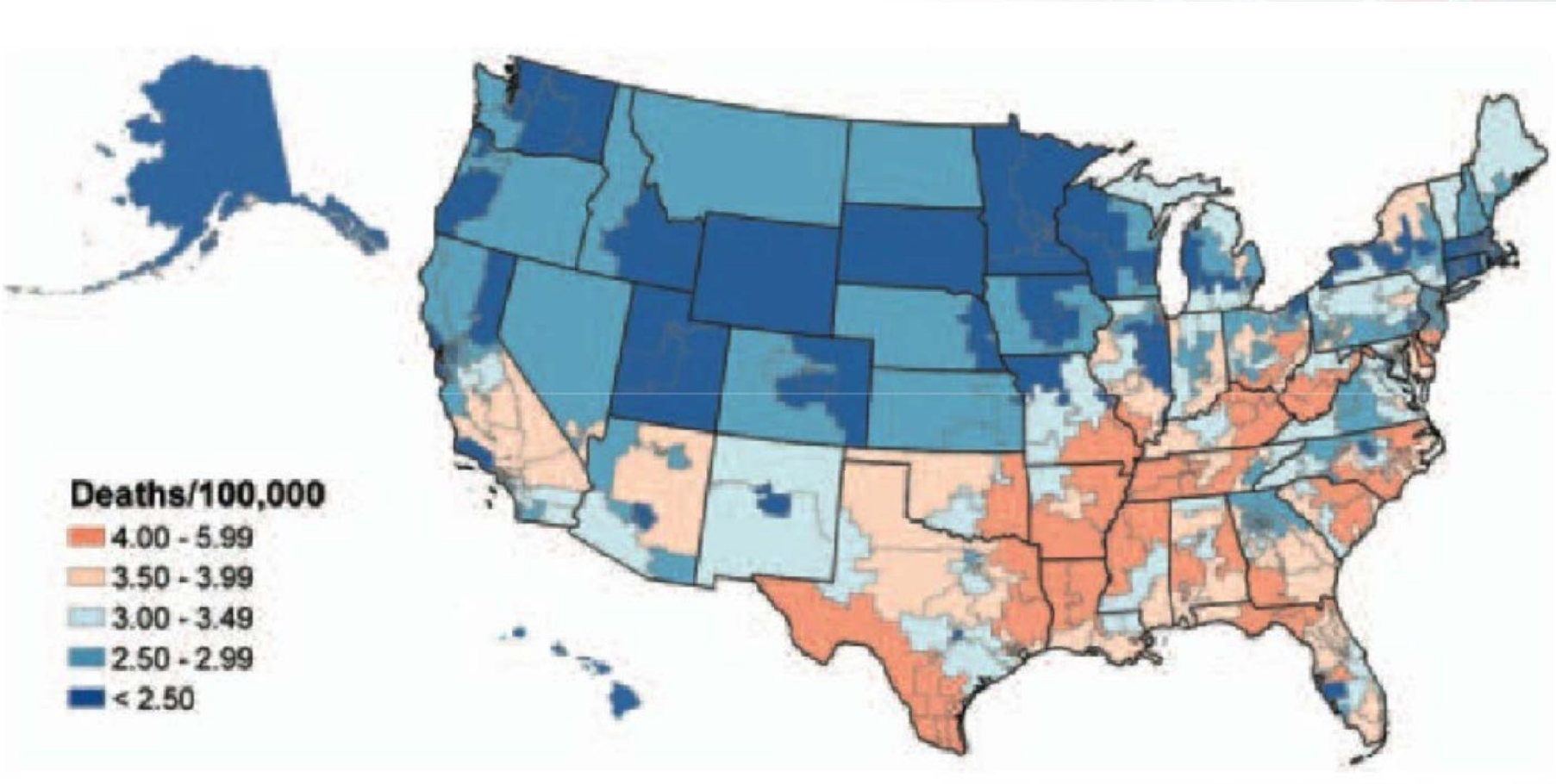
Death Rates for United States



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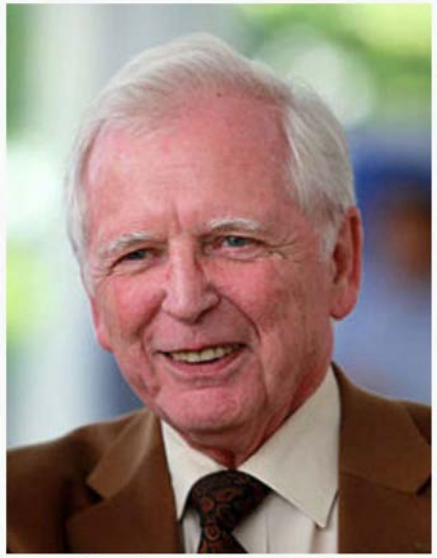
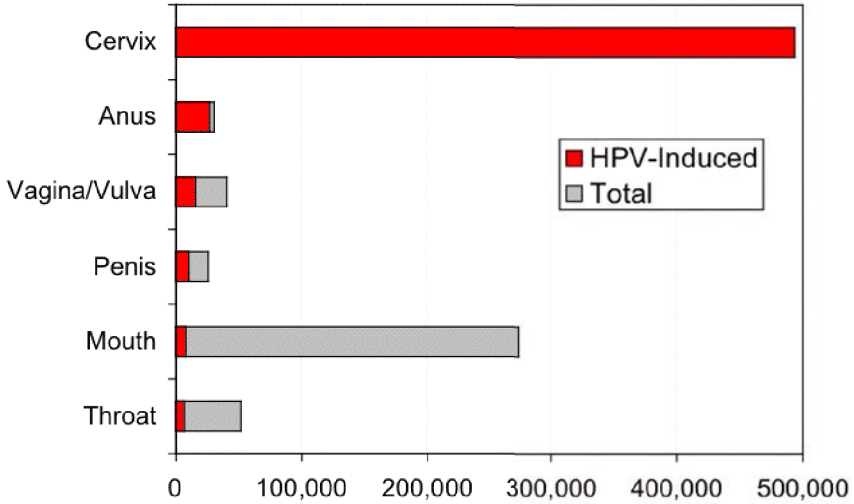
Human Papilloma Virus

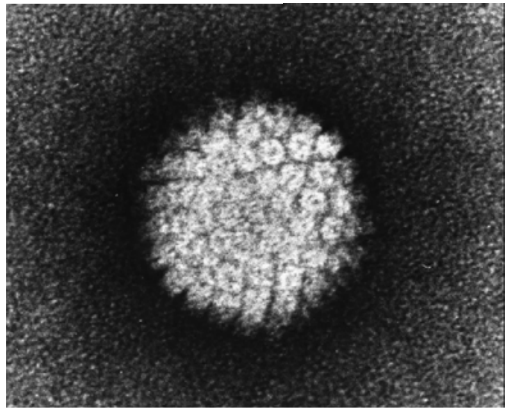
Harald zur Hausen

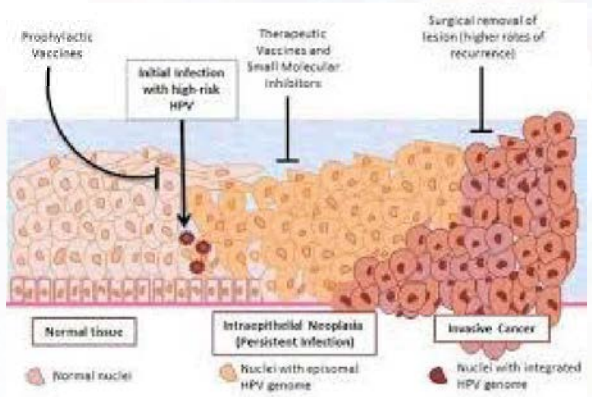


Harald zur Hausen in 2010

Born 11 March 1936 (age 83)
Gelsenkirchen, Province of Westphalia, Germany







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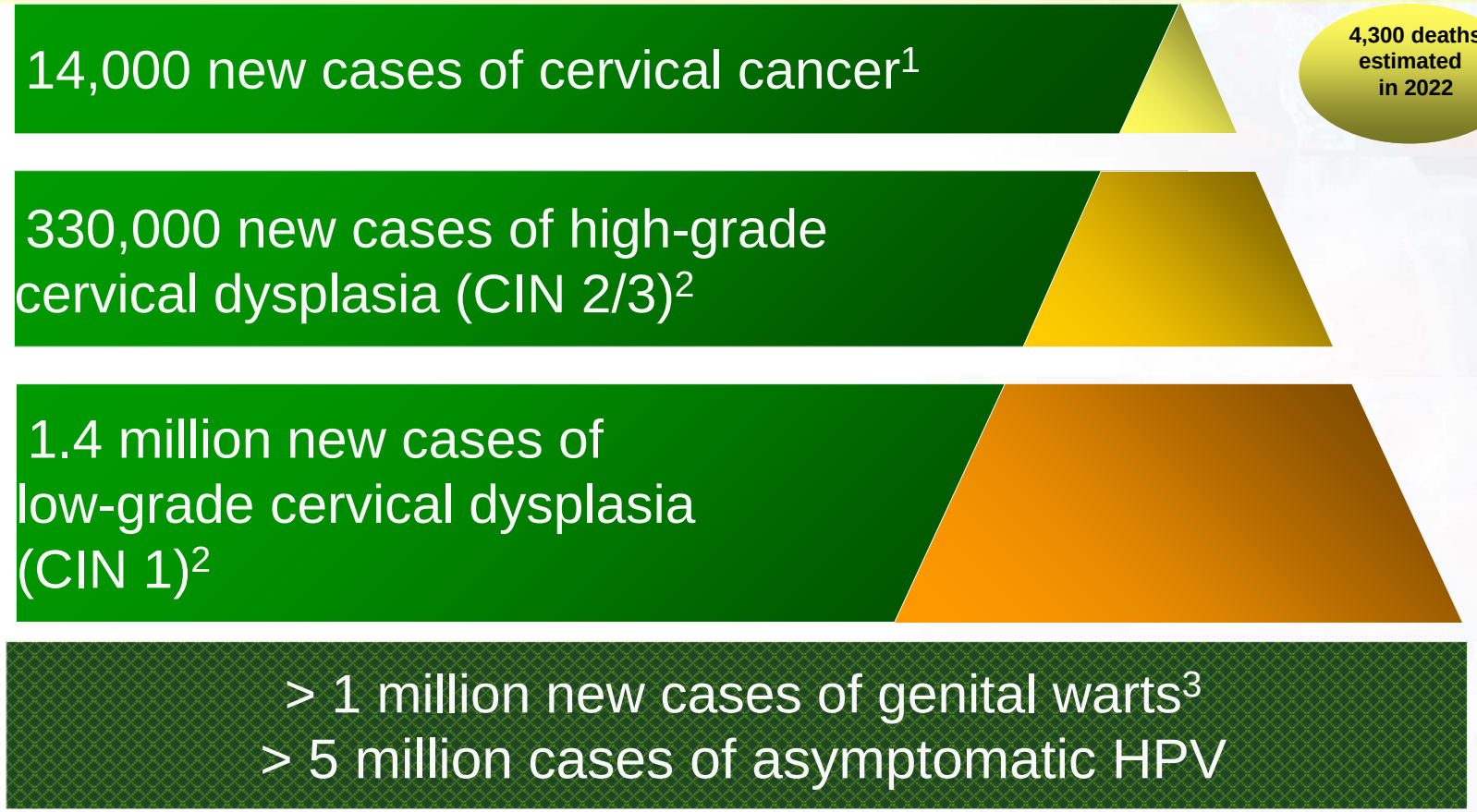
Estimated Annual Burden of HPV-Related Diagnoses in the United States

All HPV Related Cancers 55,000



1. American Cancer Society. *Cancer Facts and Figures 2023.* Atlanta, Ga: American Cancer Society; 2006:4. **2**. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med*. 2003;127:946–949.
3. Fleischer AB, Parrish CA, Glenn R, Feldman SR. Condylomata acuminata (genital warts):Patient demographics and treating physicians. *Sex Transm Dis*. 2001;28:643–647.

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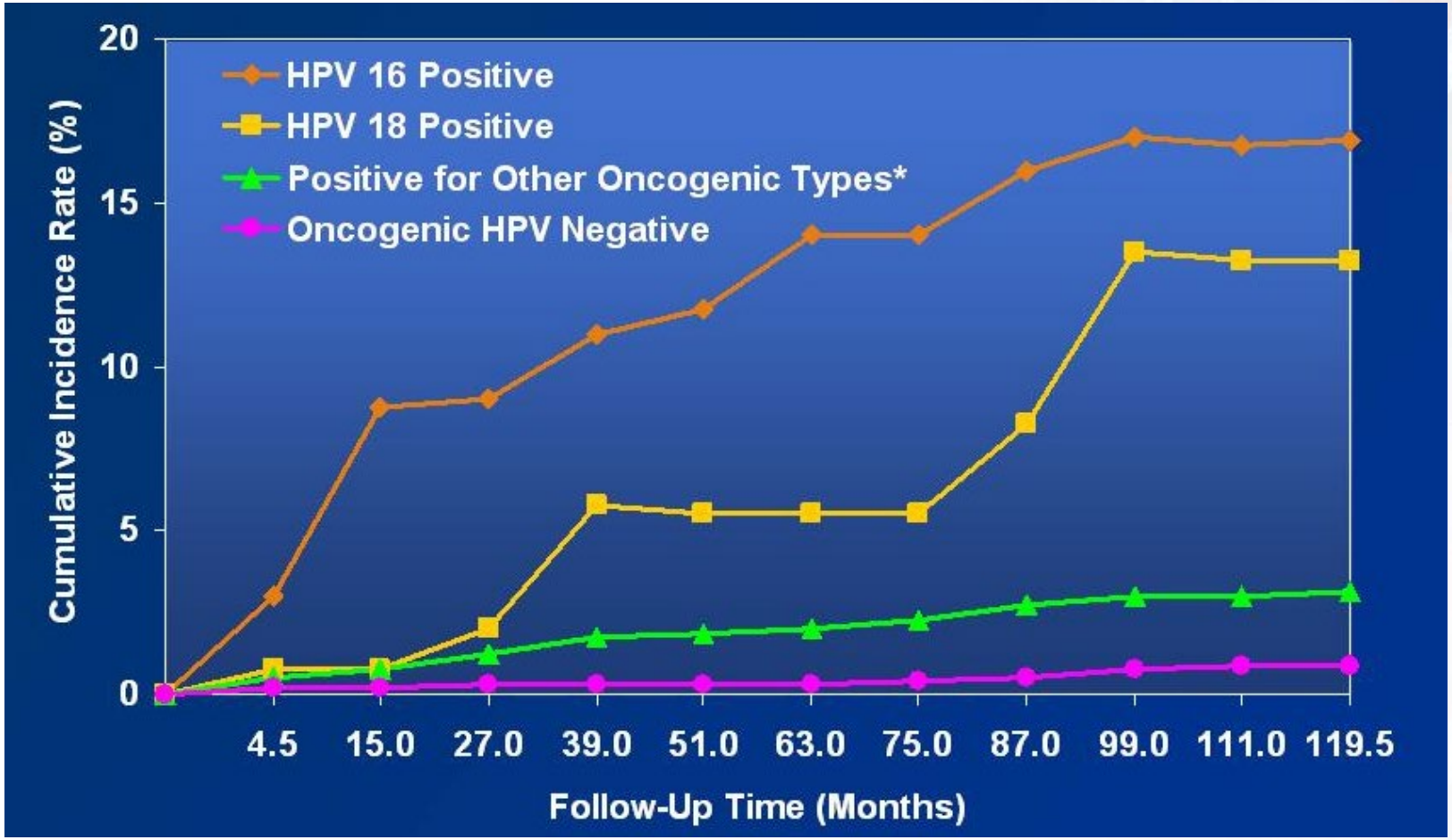
Risk of HPV infection progressing to a High Grade Lesions



Kahn MJ, J Natl Cancer Inst 97:1072: 2005

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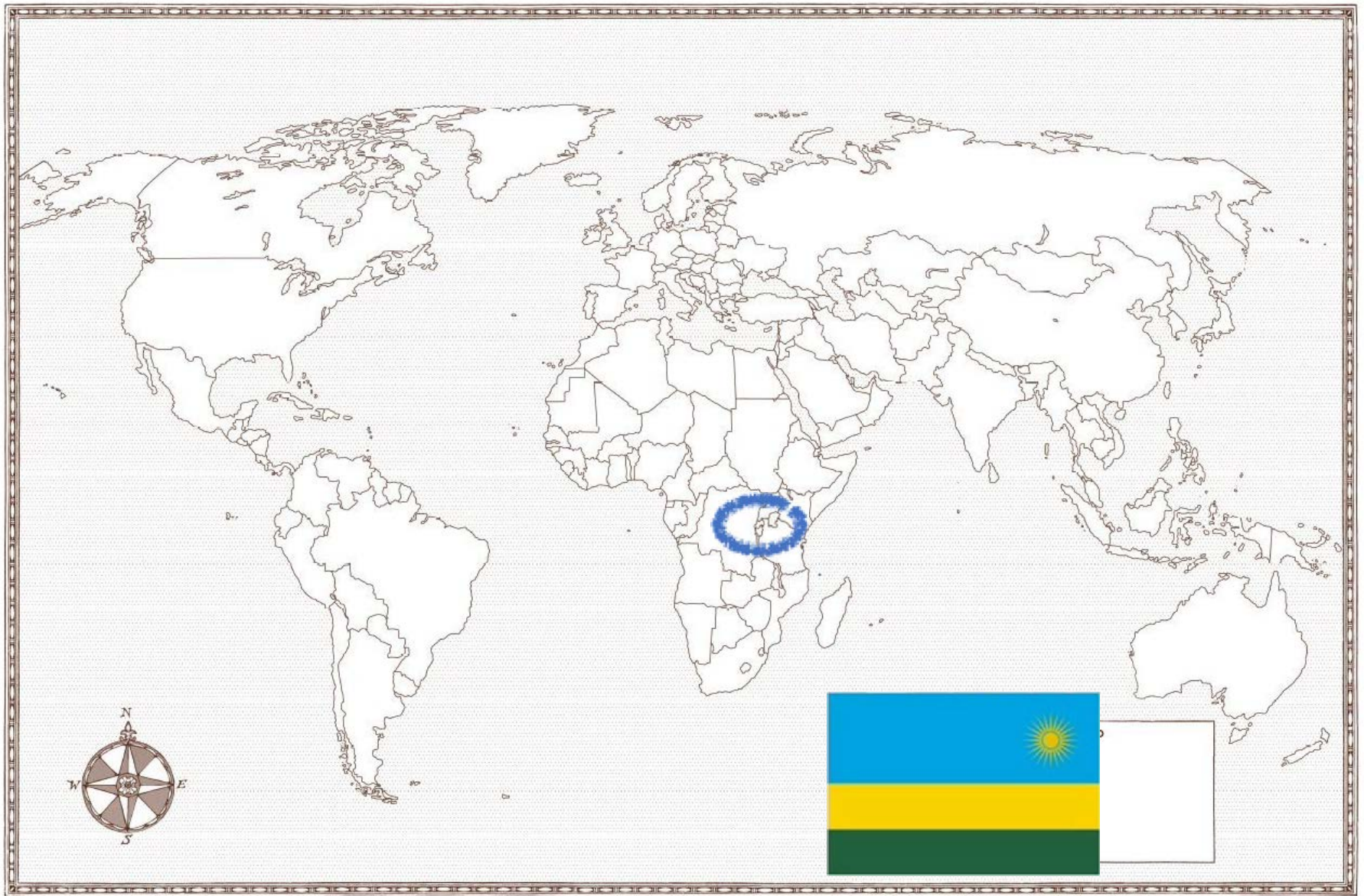
HPV Vaccination 100% Efficacious Against HPV 16/18-related CIN 2/3 or AIS

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 005*	755	0	750	12	**100%**	65.1–100
Protocol 007	231	0	230	1	**100%**	-3734.9–100
FUTURE I	2,200	0	2,222	19	**100%**	78.5–100
FUTURE II	5,301	0	5,258	21	**100%**†	80.9–100
Combined protocols	**8,487**	**0**	**8,460**	**53**	**100%**†	**92.9–100**

†P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); and efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols).

What Country has the Highest HPV Vaccination Rate?



Integration of comprehensive women's health programmes into health systems: cervical cancer prevention, care and control in Rwanda

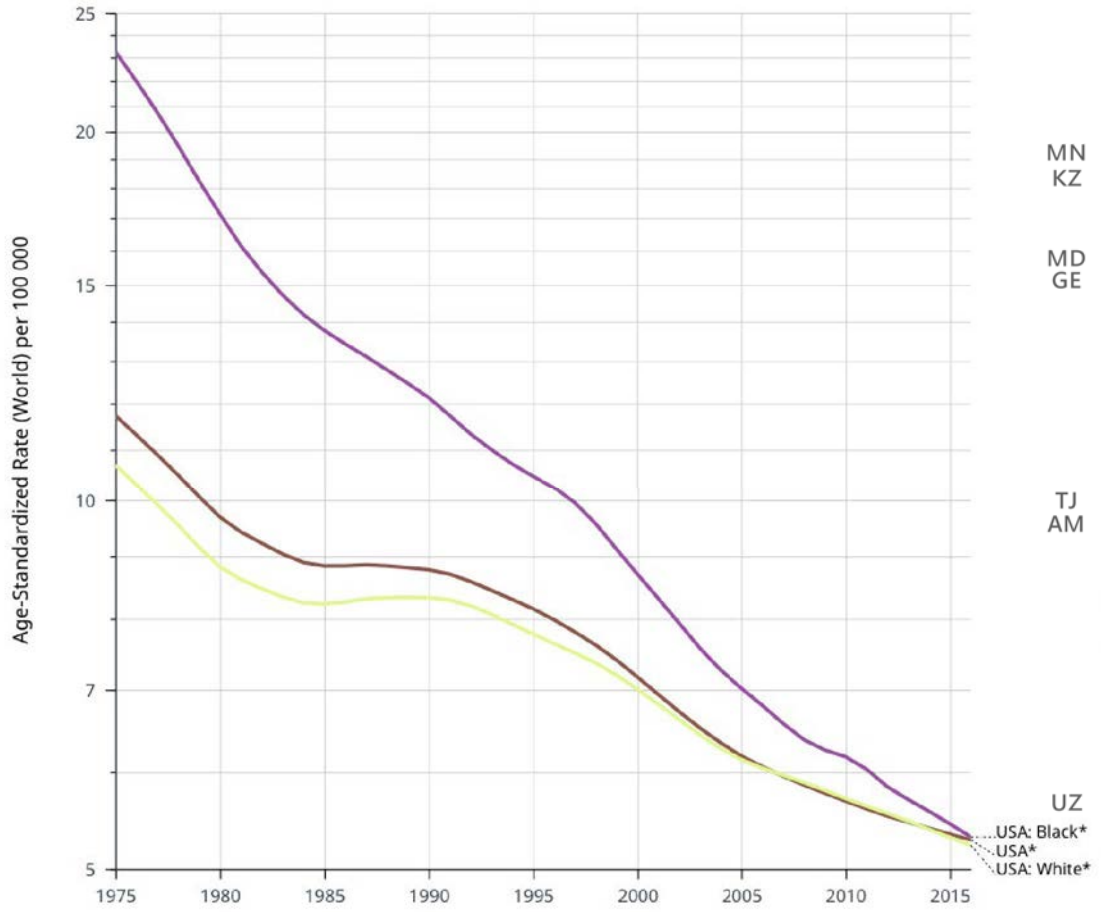
Agnes Binagwaho,[a] Fidele Ngabo,[a] Claire M Wagner,[b] Cathy Mugeni,[a] Maurice Gatera,[c] Cameron T Nutt[d] & Sabin Nsanzimana[c]

Problem Although it is highly preventable and treatable, cervical cancer is the most common and most deadly cancer among women in Rwanda.
Approach By mobilizing a diverse coalition of partnerships, Rwanda became the first country in Africa to develop and implement a national strategic plan for cervical cancer prevention, screening and treatment.
Local setting Rwanda – a small, landlocked nation in East Africa with a population of 10.4 million – is well positioned to tackle a number of "high-burden" noncommunicable diseases. The country's integrated response to infectious diseases has resulted in steep declines in premature mortality over the past decade.
Relevant changes In 2011–2012, Rwanda vaccinated 227 246 girls with all three doses of the human papillomavirus (HPV) vaccine. Among eligible girls, three-dose coverage rates of 93.2% and 96.6% were achieved in 2011 and 2012, respectively. The country has also initiated nationwide screening and treatment programmes that are based on visual inspection of the cervix with acetic acid, testing for HPV DNA, cryotherapy, the loop electrosurgical excision procedure and various advanced treatment options.
Lessons learnt Low-income countries should begin to address cervical cancer by integrating prevention, screening and treatment into routine women's health services. This requires political will, cross-sectoral collaboration and planning, innovative partnerships and robust monitoring and evaluation. With external support and adequate planning, high nationwide coverage rates for HPV vaccination and screening for cervical cancer can be achieved within a few years.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Binagwaho A, Bull World Health Org 91(9):697

Age Standardize Incidence of Cervical Cancer United States



https://gco.iarc.fr/today/online

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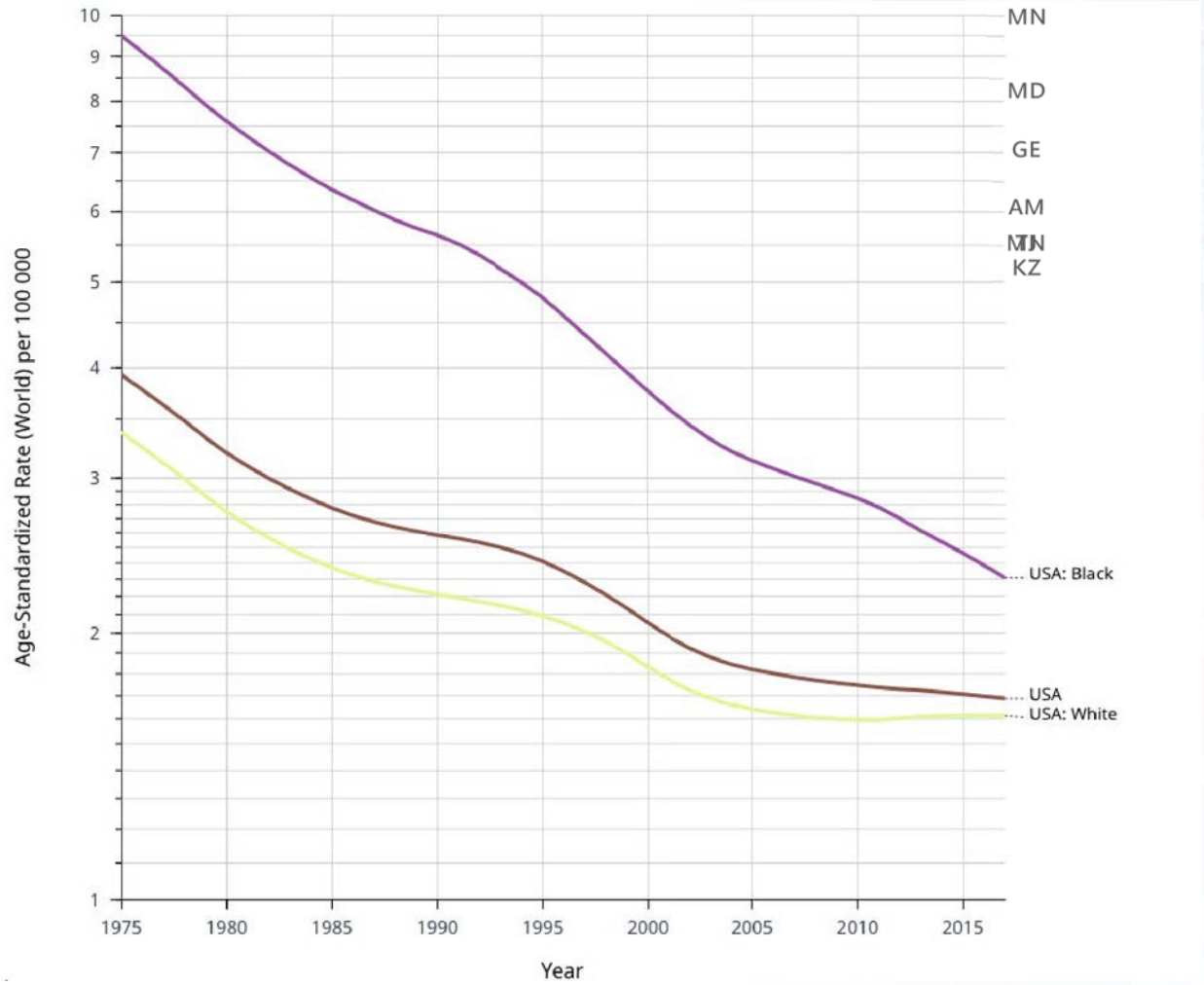
Age Standardize Mortality of Cervical Cancer
United States



https://gco.iarc.fr/today/online

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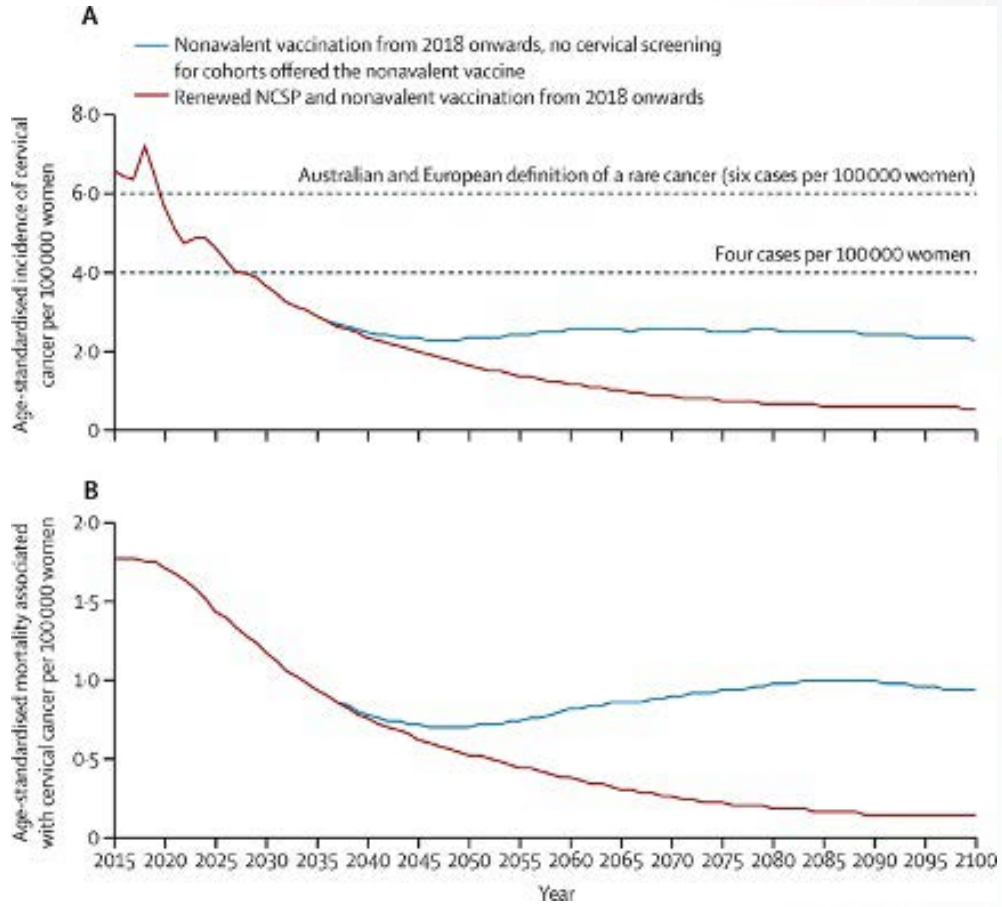
Making Cervical Cancer a Rare Disease



Hall MT, Lancet Public Health 2019; 4: e19–27

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Treatment of Cervical Cancer

Radical Hysterectomy

- First described by John Clark (under Howard Kelly) in 1895
- 1898 Ernst Wertheim combined this surgery with removal of the lymphatics
  - In 1905 reported the first 270 operations
    - 18% mortality
    - 31% major morbidity
  - In 1912 published on 500 operations
    - His name became associated with this operation

Maria Sklodowska Curie

- Born in Poland
- Worked in Paris
- Isolated Radium for medical treatment in 1910 for the treatment of cervical cancer

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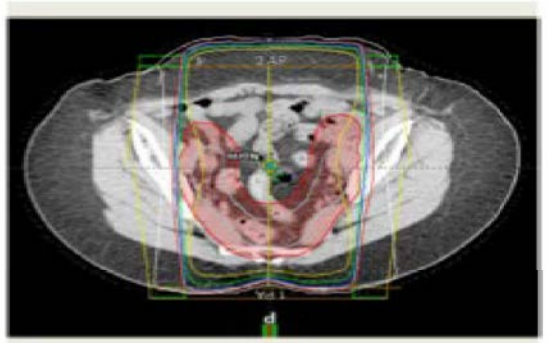
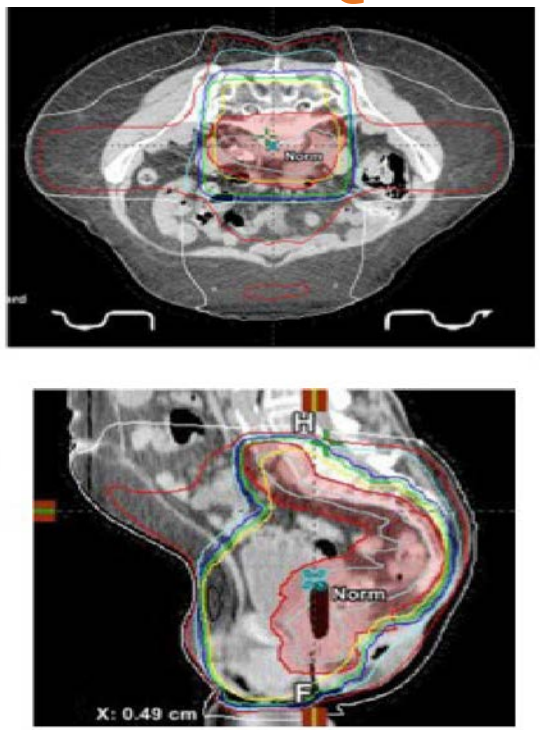
Evolution of Pelvic Radiation

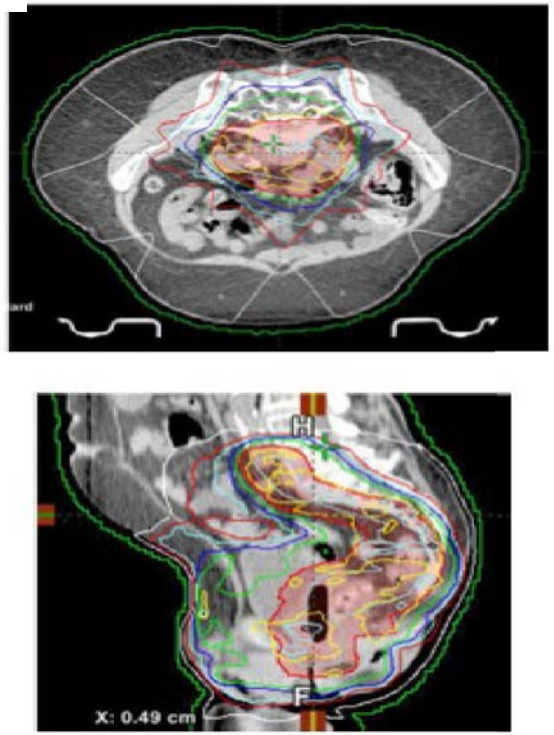
TECHNIQUES



APP/PA Fields



3D Conformal



IMRT

Joe Vincent Meigs (1892-1963)

- Meigs revived the modified radical hysterectomy in 1944
- Showed a 75% survival with a 1% mortality rate when performed by an expert surgeon

FIGO Stage 2018[a]

I Confined to cervix (extension to uterine corpus should be disregarded)

1A Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm

- **1A1** Measured stromal invasion <3 mm in depth (LVSI +/-)
- **1A2** Measured stromal invasion ≥3 mm and < 5 mm in depth (LVSI +/-)

1B Invasive carcinoma with deepest invasion ≥ 5 mm (greater than stage 1A); lesion limited to th cervix

- **1B1** Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
- **1B2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
- **1B3** Invasive carcinoma ≥4 cm in greatest dimension

SURGERY

II Invades beyond the uterus, but has not extended onto the lower third of the vagina or to the wall

RADIATION

IIA Involvement limited to upper two-thirds of vagina without parametrial involvement

- **IIA1** Invasive carcinoma <4 cm in greatest dimension
- **IIA2** Invasive carcinoma ≥4 cm in greatest dimension

IIB With parametrial involvement but not up to pelvic wall

[a]Imaging evaluation may now be used in addition to clinical assessment where resources permit
LVSI, lymphovascular space invasion

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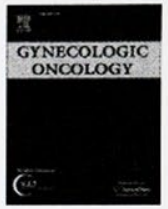
Less radical surgery

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

Kathleen M. Schmeler *, Michael Frumovitz, Pedro T. Ramirez

Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, 1155 Herman Pressler Drive, Houston, TX 77030, USA

Author	Year	Low-risk criteria	N	Parametrial involvement in low-risk group (%)
Kinney [13]	1995	Squamous histology only, tumor <2 cm, no LVSI*	83	0.0%
Covens [14]	2002	All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes	536	0.6%
Stegeman [15]	2007	Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes	103	0.0%
Wright [16]	2008	All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes	270	0.4%
Frumovitz [19]	2009	Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI*	125	0.0%

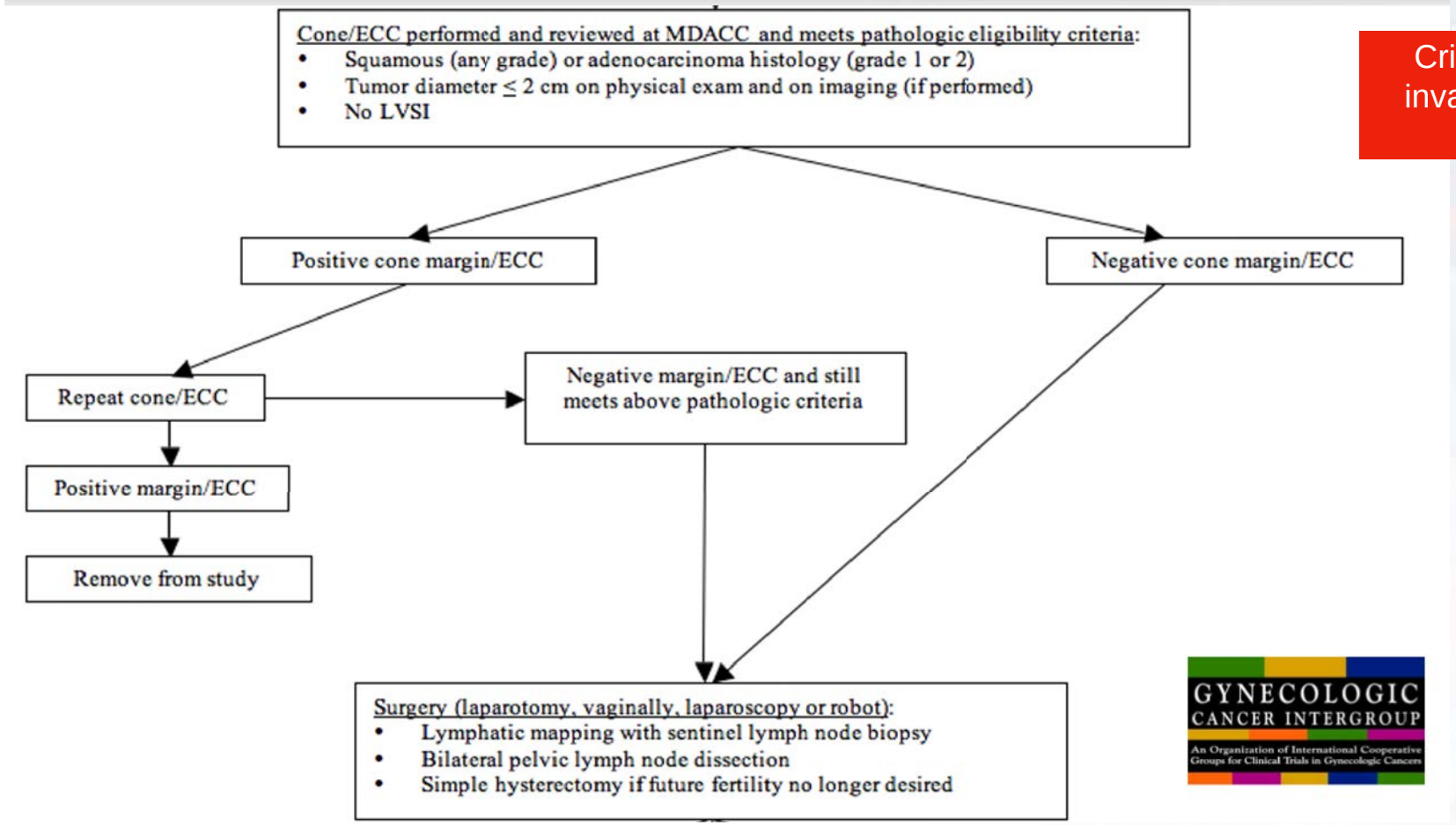
*LVSI: lymphvascular space involvement
**DOI: depth of invasion

All retrospective data

N=1117 < 1%

Schmeler K et al. Gynecol Oncol 120:321, 2011

ConCerv Trial



Criteria modified to <10 mm invasion after recurrence in a patient with 14 mm

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

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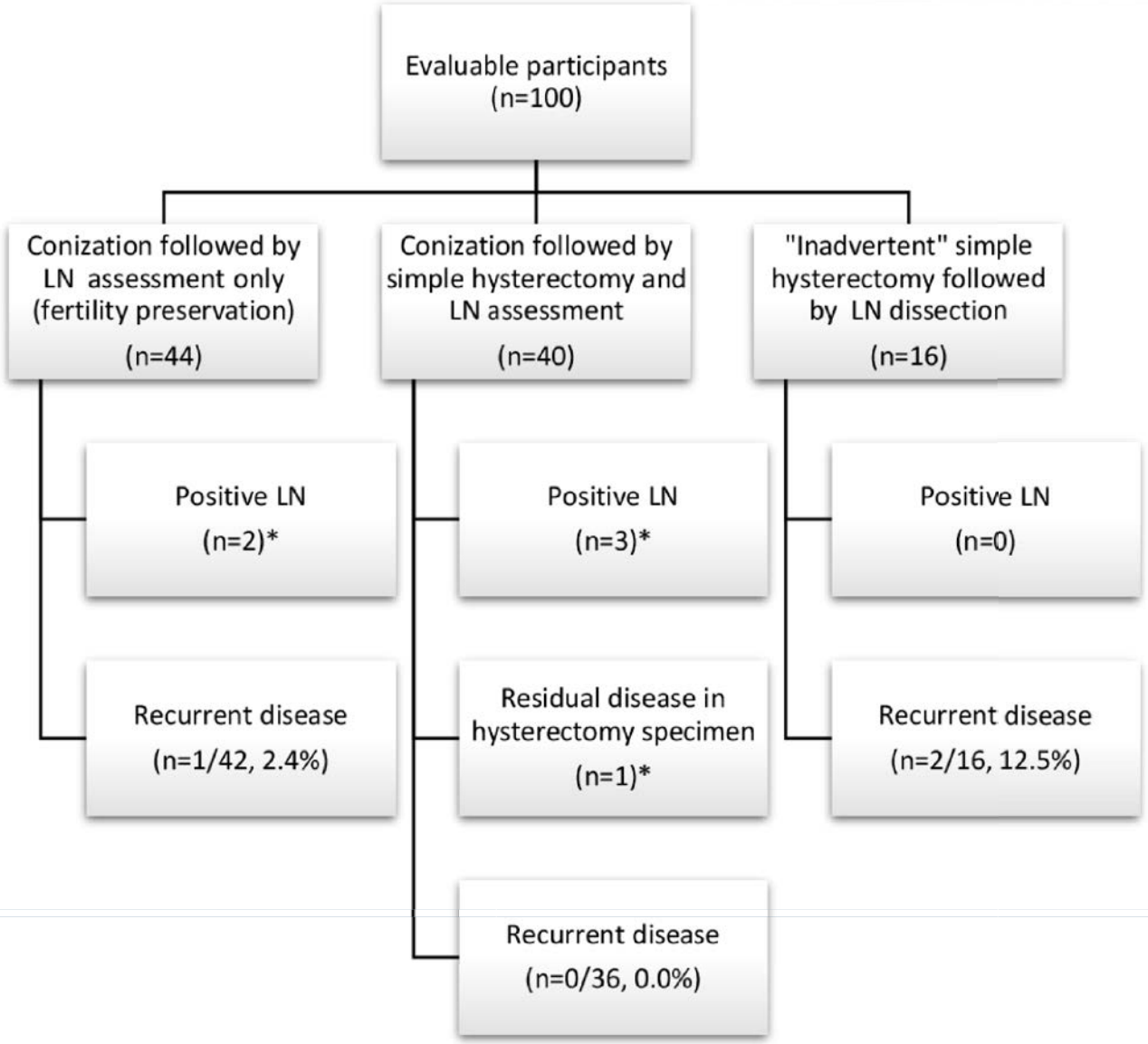
ConCerv Trial

90% of Surgeries MIV



Schmeler KM, Int J Gynecol Cancer. 2023;33(4):498-503

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2023 ASCO ANNUAL MEETING

GCIG GYNECOLOGIC CANCER INTERGROUP

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer

A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group

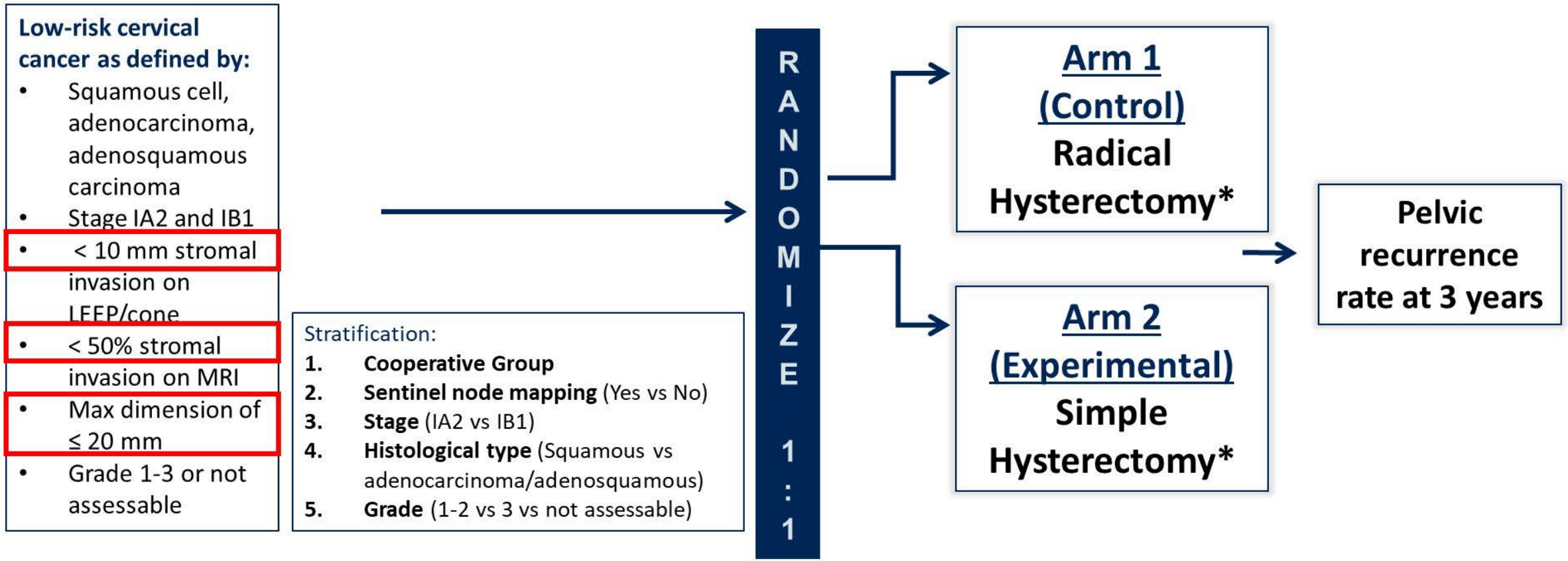
CCTG CX.5 - SHAPE

NCT01658930

Marie Plante, Janice Kwon, Sarah Ferguson, Vanessa Samouelian, Gwenael Ferron, Amandine Maulard, Cor de Kroon, Willemien Van Driel, John Tidy, Sven Mahner, Stefan Kommoss, Frederic Goffin, Christian Marth, Karl Tamussino, Brynhildur Eyjolfsdottir, Jae-Weon Kim, Noreen Gleeson, Juliana Ubi, Lori Brotto, Dongsheng Tu, Lois Shepherd

On behalf of the SHAPE investigators

Trial Schema

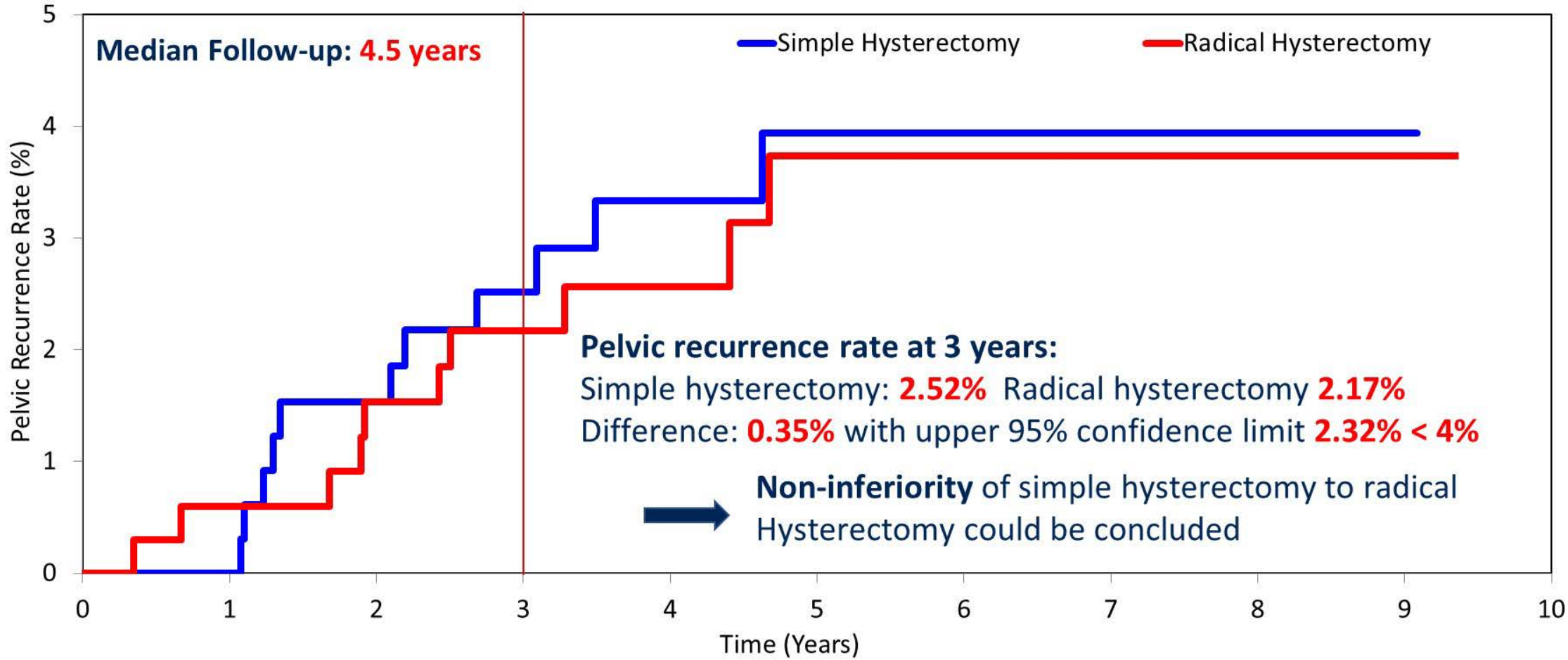


*Regardless of treatment assignment, surgery will include **pelvic lymph node dissection** with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

All Treated Patients Post Surgery

Adjuvant Treatment	Simple hysterectomy N=338 (%)	Radical hysterectomy N=344 (%)	P-value
• **Adjuvant Post Operative Treatment**	31 (9.2)	29 (8.4)	0.79
• Chemotherapy only	1	0	
• Radiation therapy only	15	11	
• Chemoradiation	15	18	

Pelvic Recurrence Rate (ITT)



Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

Secondary Efficacy Endpoints (ITT)

Endpoints	Simple Hysterectomy N=350	Radical Hysterectomy N=350		
	3 year outcomes		Hazard Ratio (90% confidence interval)	P-value
Pelvic Recurrence Free Survival	97.5%	97.8%	1.12 (0.54-2.32)	0.79
Extra-Pelvic Recurrence Free Survival	98.1%	99.7%	3.82 (0.79-18.4)	0.10
Relapse Free Survival	96.3%	97.8%	1.54 (0.69-3.45)	0.30
Overall Survival	99.1%	99.4%	1.09 (0.38-3.14)	0.87

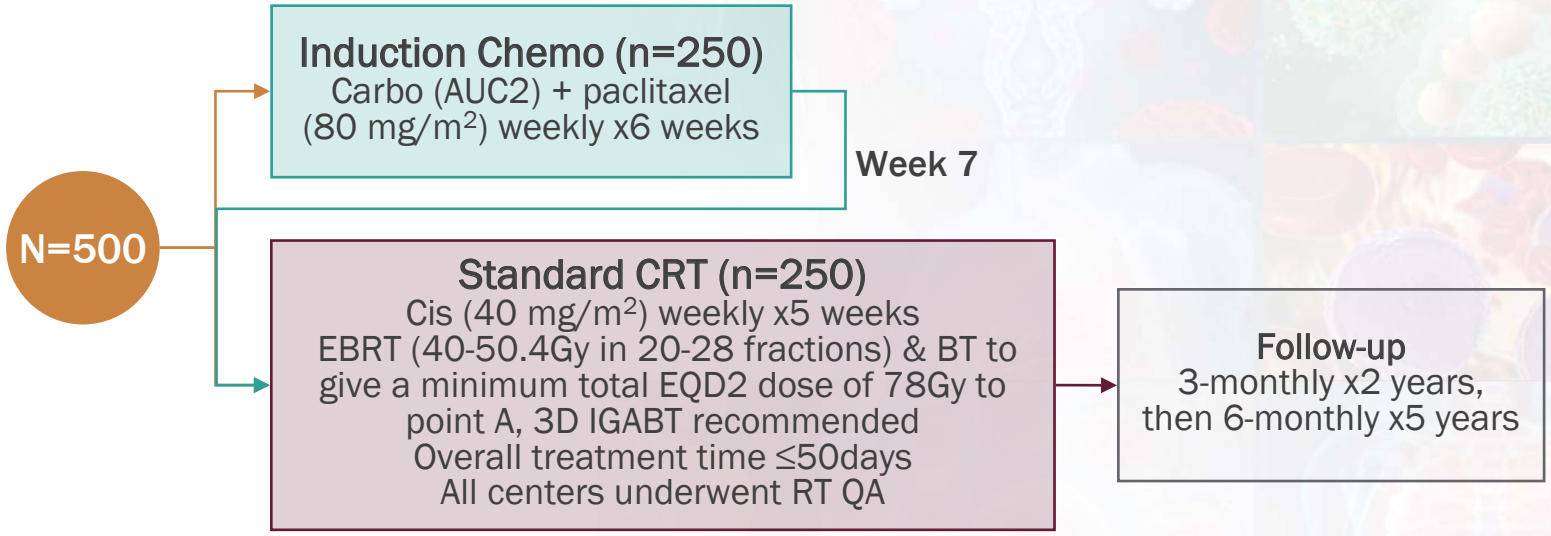
Surgery-Related Adverse Events (All Grades with incidence ≥ 5% in one of the Arms)

Adverse Event	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value
	Within 4 weeks of surgery (acute)			After 4 weeks of surgery (late)		
Any adverse event	144 (42.6)	174 (50.6)	**0.04**	181 (53.6)	208 (60.5)	**0.08**
• Abdominal pain	33 (9.8)	42 (12.2)	0.33	36 (10.7)	47 (13.7)	0.24
• Constipation	16 (4.7)	22 (6.4)	0.40	13 (3.8)	19 (5.5)	0.37
• Fatigue	19 (5.6)	23 (6.7)	0.63	19 (5.6)	28 (8.1)	0.23
• Paresthesia	14 (4.1)	22 (6.4)	0.23	17 (5.0)	22 (6.4)	0.51
• Peripheral sensory neuropathy	- (-)	- (-)	- (-)	21 (6.2)	13 (3.8)	0.16
• Urinary incontinence	8 (2.4)	19 (5.5)	**0.048**	16 (4.7)	38 (11.0)	**0.003**
• Urinary retention	2 (0.6)	38 (11.0)	**<0.0001**	2 (0.6)	34 (9.9)	**<0.0001**
• Dyspareunia	- (-)	- (-)	- (-)	21 (6.2)	19 (5.5)	0.75
• Pelvic pain	19 (5.6)	9 (2.6)	0.054	23 (6.8)	17 (4.9)	0.33
• Lymphedema	- (-)	- (-)	- (-)	35 (10.4)	36 (10.5)	1.00
• Hot flashes	- (-)	- (-)	- (-)	14 (4.1)	20 (5.8)	0.38

INTERLACE: Phase 3 Trial of Induction Chemo Followed by Chemoradiation

- FIGO (2008) stages IB1 node+, IB2, II, IIIB, IVA cervical cancer
- No nodes above aortic bifurcation on imaging
- Fit for Chemo and radical RT
- No prior pelvic RT

- Stratification factors: site, stage, nodal status, 3D-conformal vs IMRT EBRT, 2D vs 3D brachytherapy, tumor size, SCC vs other.



Endpoints
- Primary: PFS and OS
- Key secondary: AEs, pattern of relapse, QOL, time to subsequent treatment

McCormack M, et al. ESMO 2023. LBA8.

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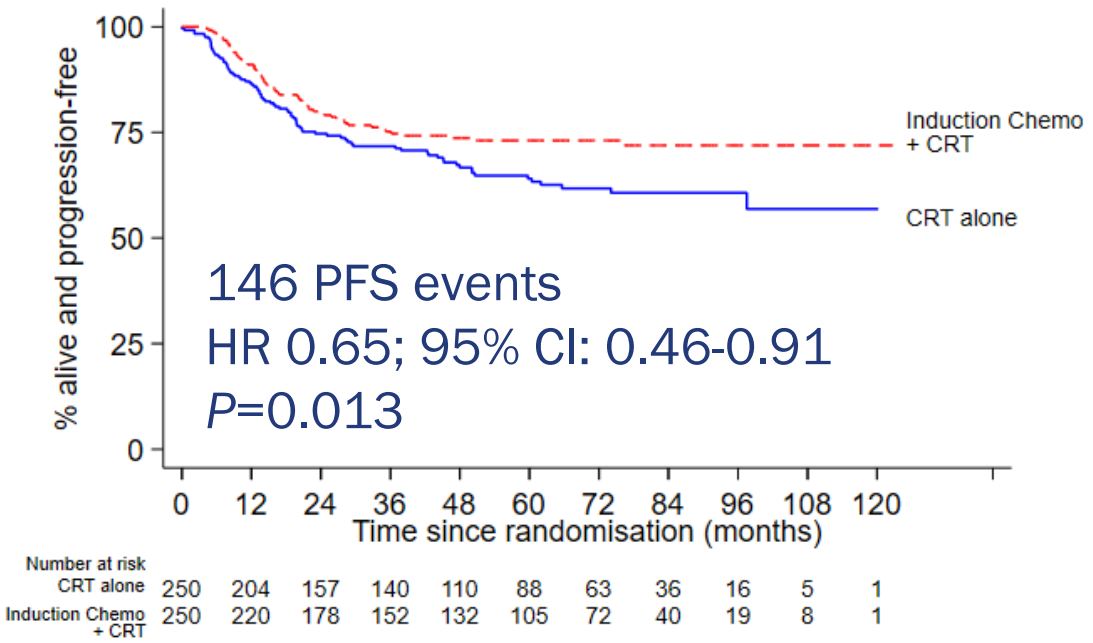
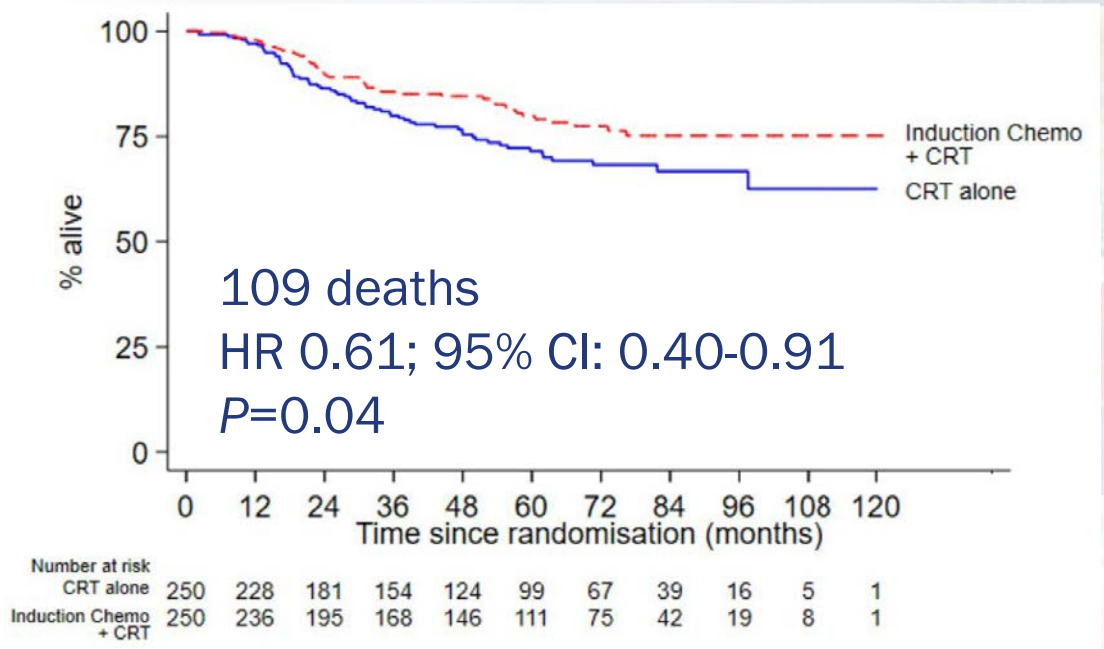
INTERLACE: PFS and OS (median follow-up 64 mo)





	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

McCormack M, et al. ESMO 2023. LBA8.

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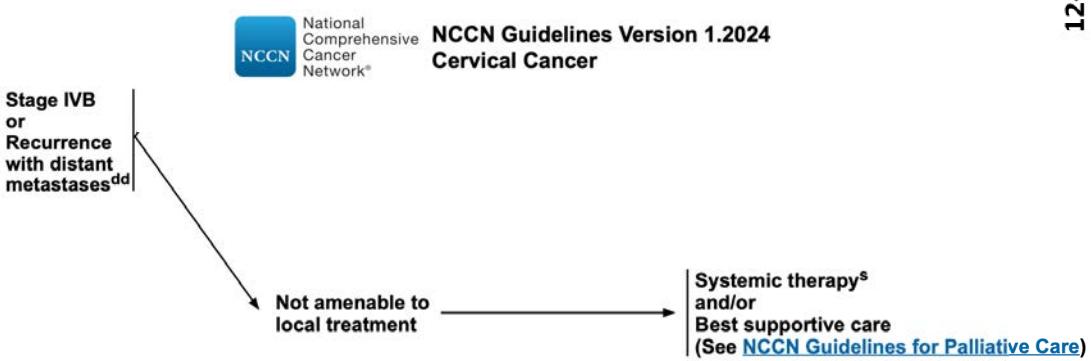
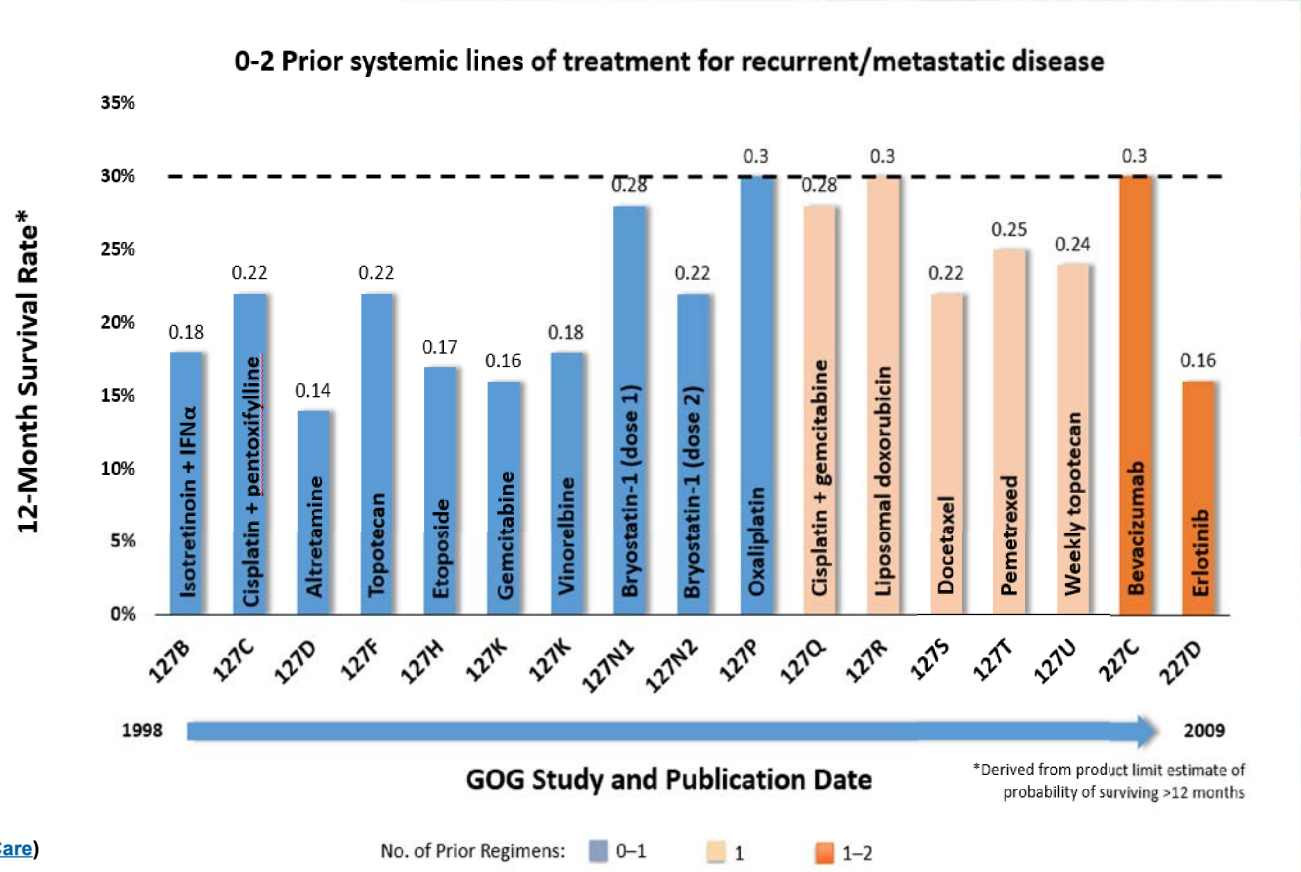
Recurrent Disease

Chemotherapy Regimens

- Phase 2 studies (1998-2010)
  - 12-month OS rate: ~30% (at best)
- Second-line therapies with minimal efficacy
- Highlights the need for new therapeutics





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GOG 240 A Randomized Phase III Trial of Cisplatin plus Paclitaxel with and without Bevacizumab vs. the Non-Platinum doublet, Topotecan plus Paclitaxel, with or without Bevacizumab in advanced or recurrent Cervical Cancer

Primary Endpoints:
- Overall survival (OS)
- Frequency and severity of toxicity

Secondary Endpoints:
- Progression-free survival (PFS)
-Tumor response

Stage IVB, persistent or recurrent cervical cancer

n ~ 450

RANDOMIZE

Stratified
- advanced vs recurrent
- performance status
- prior cisplatin for RT

Paclitaxel 135 mg/m2 IV over 24 hrs on day 1
Cisplatin 50 mg/m2 IV on day 2
OR
Paclitaxel 175 mg/m2 IV over 3 hrs on day 1
Cisplatin 50 mg/m2 IV on day 2
OR
Paclitaxel 175 mg/m2 IV over 3 hrs on day 1
Cisplatin 50 mg/m2 IV on day 1

Same + Bevacizumab 15 mg/kg q 3 wk

Paclitaxel 175 mg/m2 over 3 hrs on day 1
Topotecan 0.75 mg/m2 over 30 mins days 1-3

Same + Bevacizumab 15 mg/kg q 3 wk

Cycles repeated q21 days to progression/toxicity**

Required 346 events for HR of 0.7

Study Dates 4/09 - 1/12

Tewari KS, ASCO LBA, Chicago, 2013

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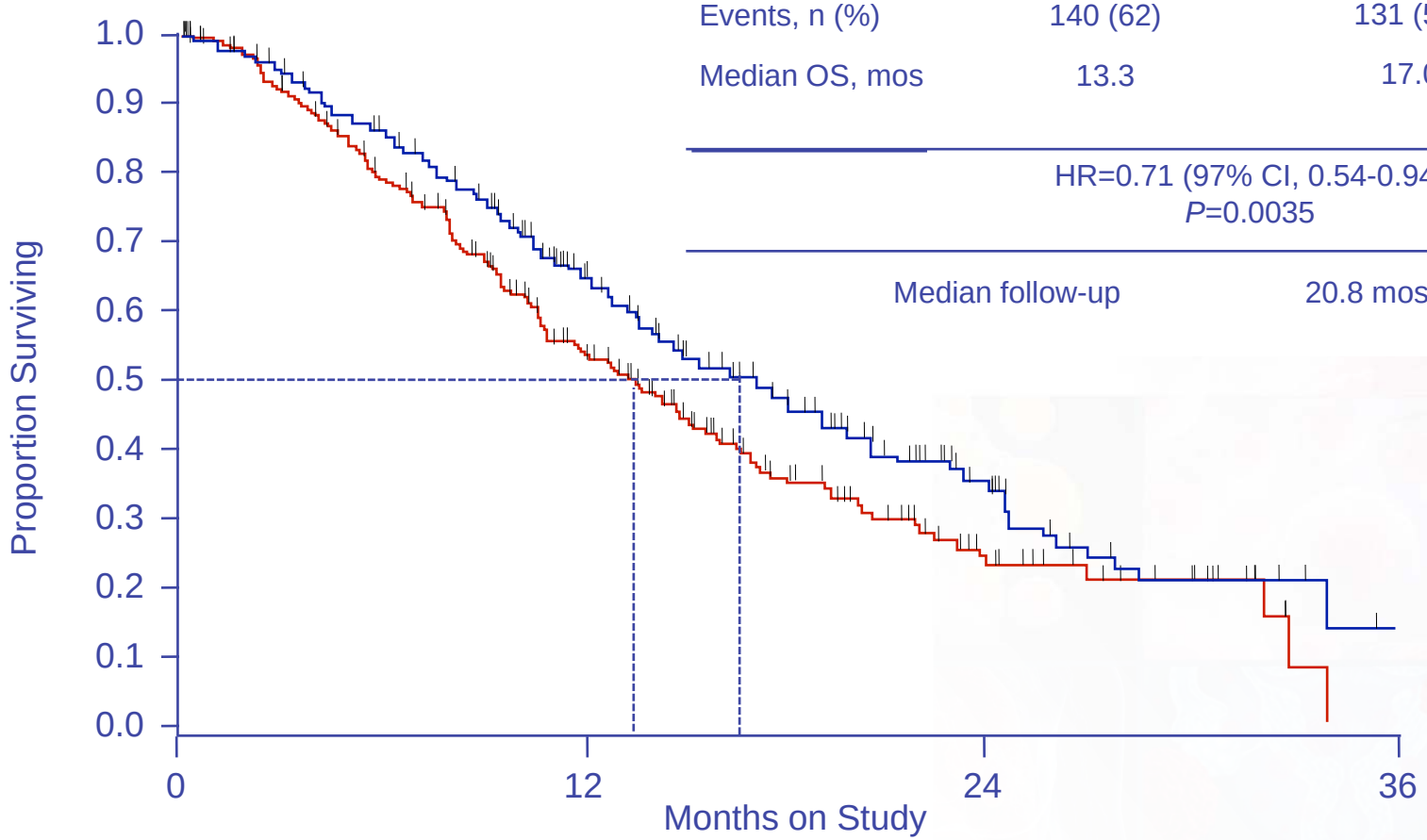
Levine Cancer Institute

GOG 240: OS for Chemo vs Chemo + Bev

	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Events, n (%)	140 (62)	131 (58)
Median OS, mos	13.3	17.0
	HR=0.71 (97% CI, 0.54-0.94) *P*=0.0035	
Median follow-up		20.8 mos



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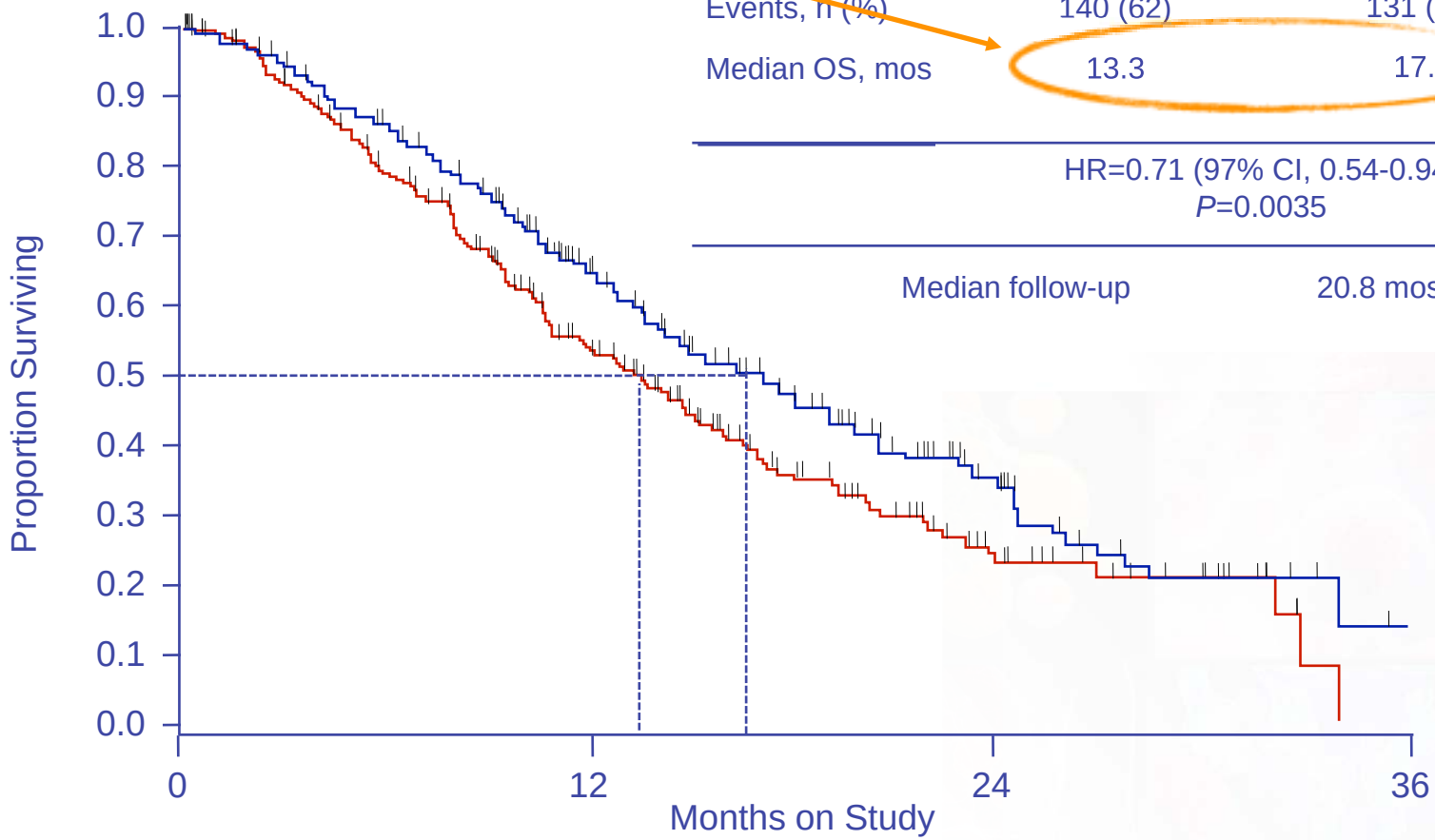
GOG 240: OS for Chemo vs Chemo + Bev

Is 3.7 month OS worth a 7% fistula rate?

	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Events, n (%)	140 (62)	131 (58)
Median OS, mos	13.3	17.0
	HR=0.71 (97% CI, 0.54-0.94) *P*=0.0035	
Median follow-up		20.8 mos



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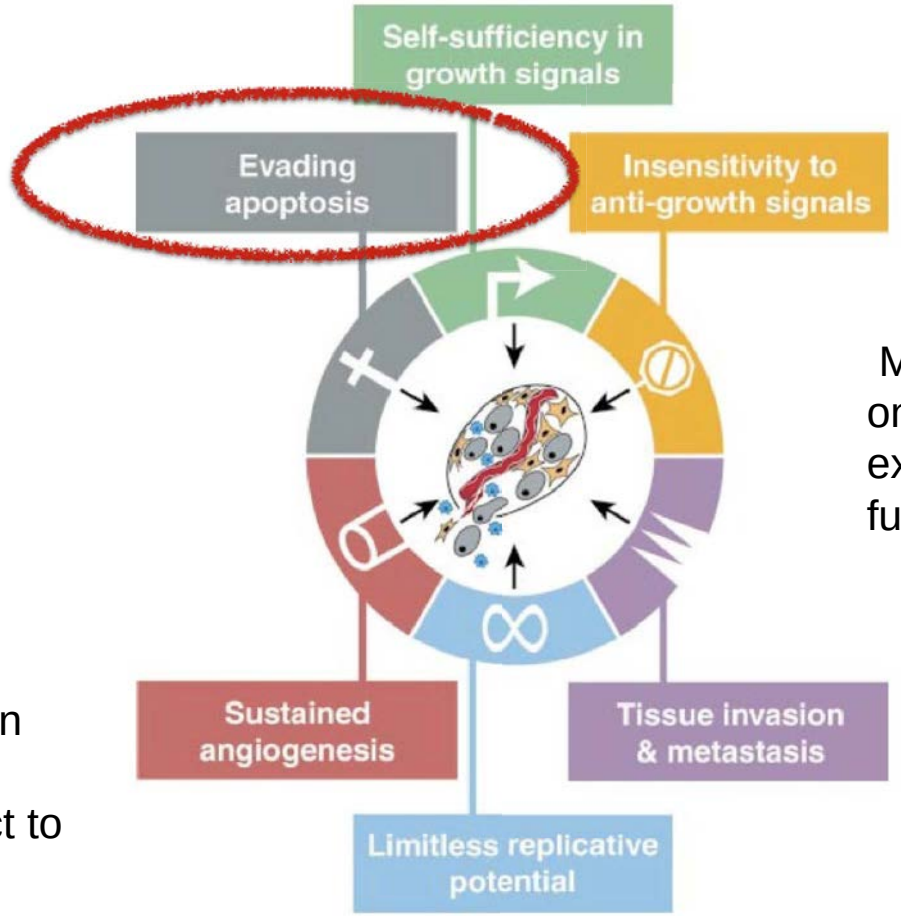
Cancer Development: Opportunities for Targeted Therapy



Most functions are related to oncogene regulation (either expression or loss of function)

Angiogenesis required by all tumors and can be regulated without respect to oncogenic mutations

Hanahan D, Cell 100(1):57, 2000

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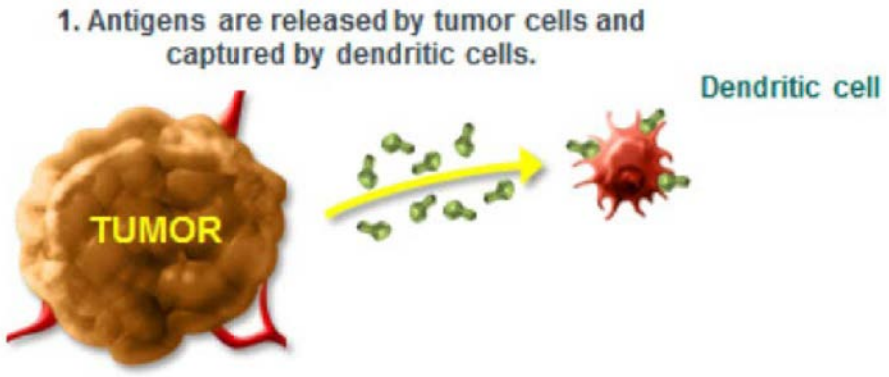
Tumor Immune Response



May KR Jr, Cancer Immunology, 2nd Ed, Elsevier, 2013: 101

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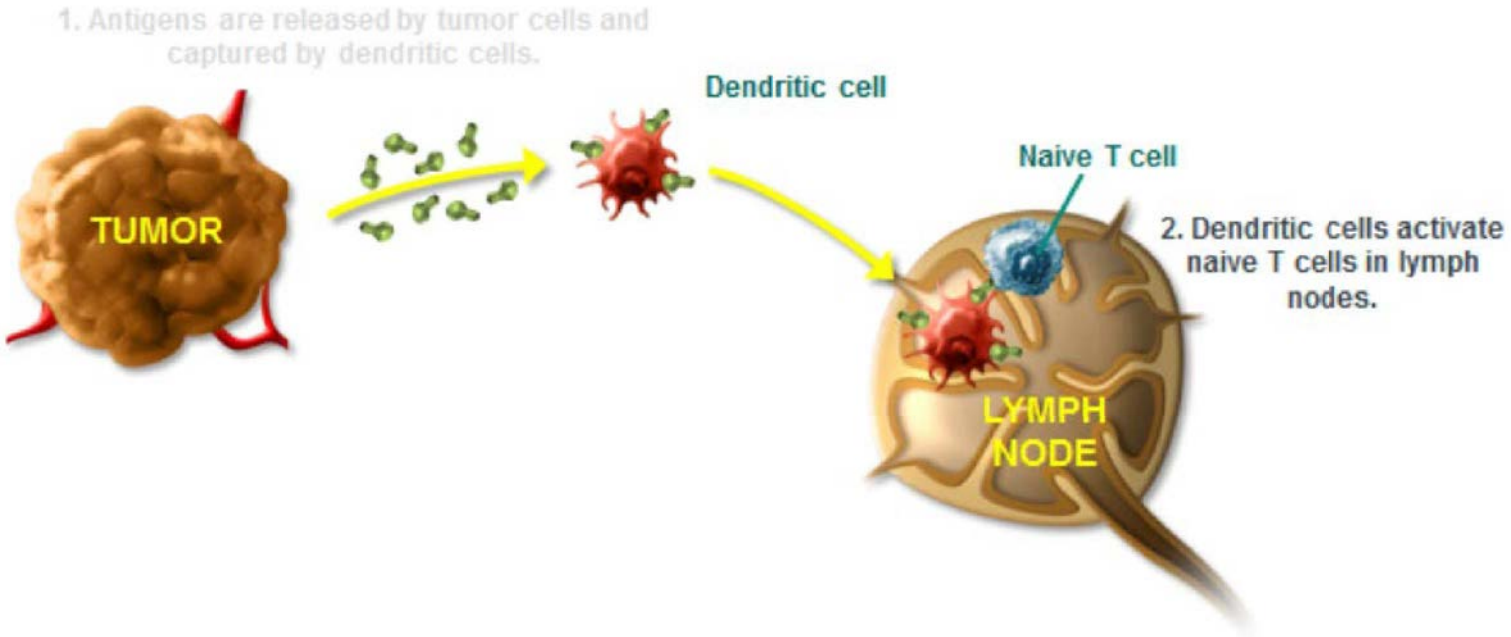
Tumor Immune Response



May KR Jr, Cancer Immunology, 2nd Ed, Elsevier, 2013: 101

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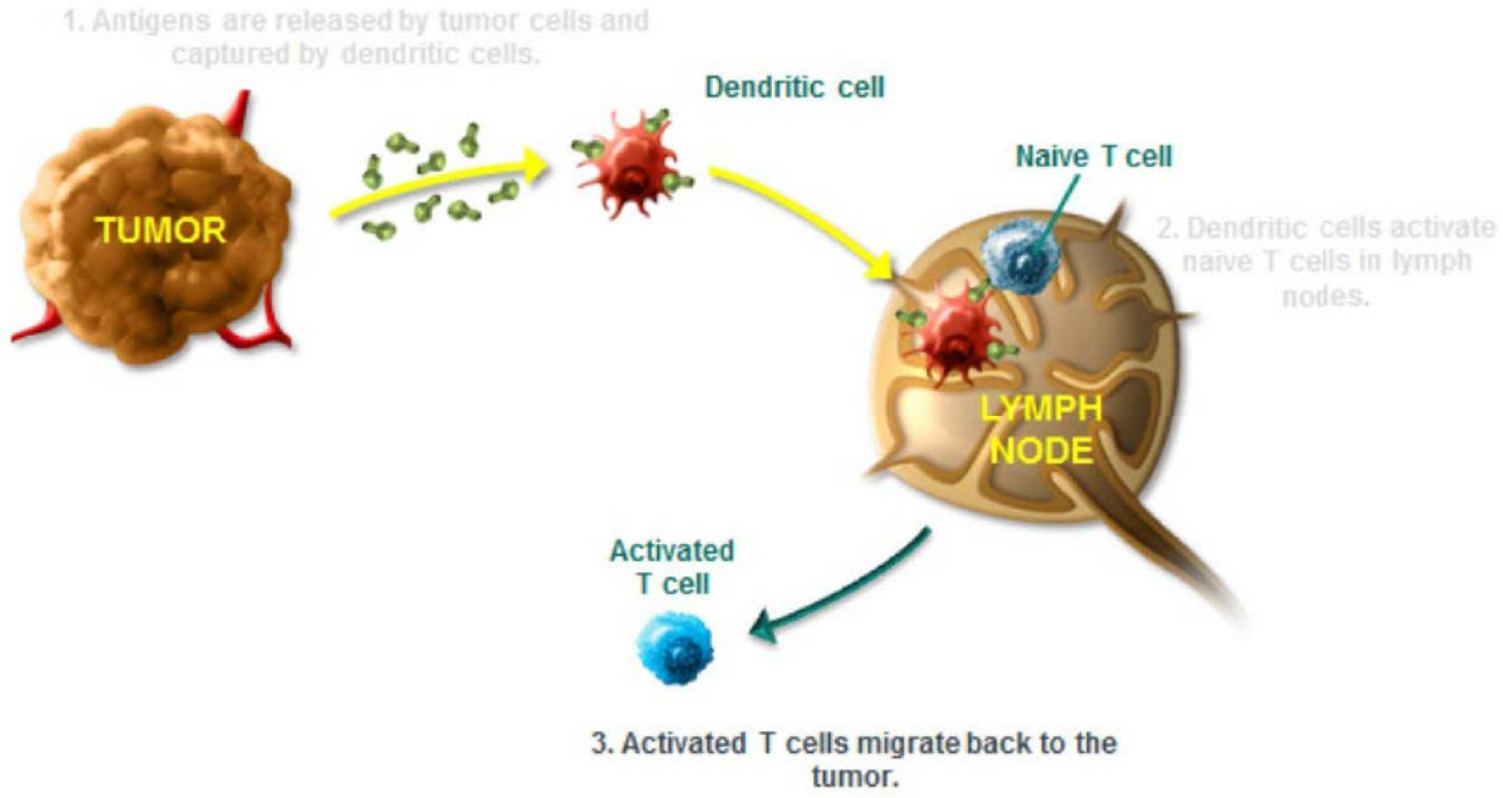
Tumor Immune Response



May KR Jr, Cancer Immunology, 2nd Ed, Elsevier, 2013: 101

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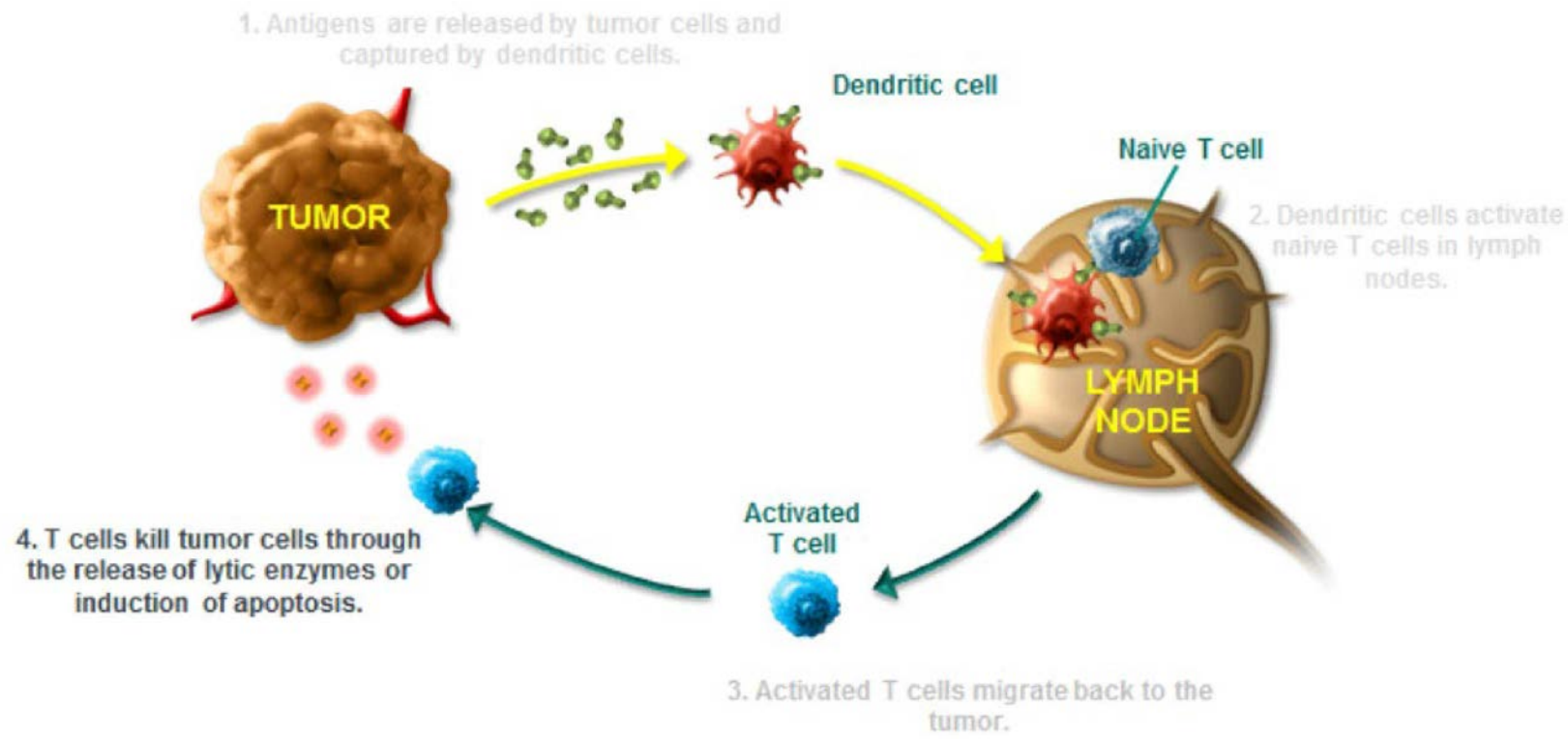
Tumor Immune Response



May KR Jr, Cancer Immunology, 2nd Ed, Elsevier, 2013: 101

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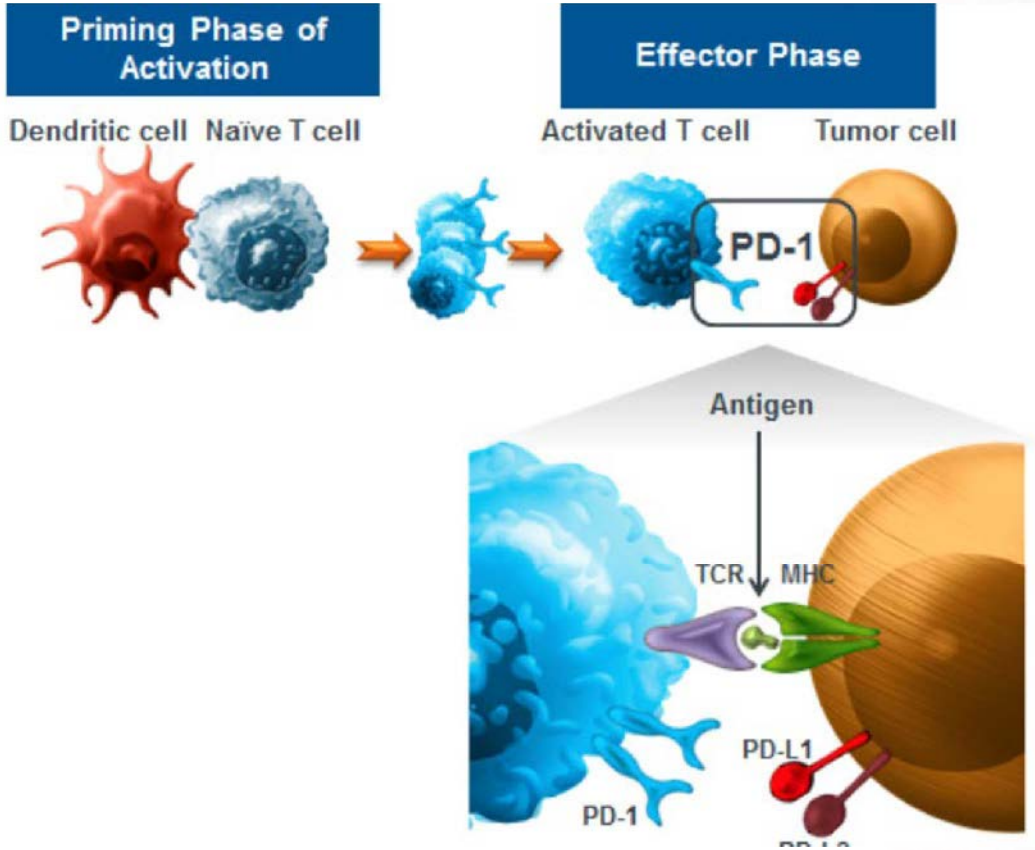
T-cell Activation and Tumor Kill



- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

Pardoll DM, Nat Rev Cancer 12:252, 2012

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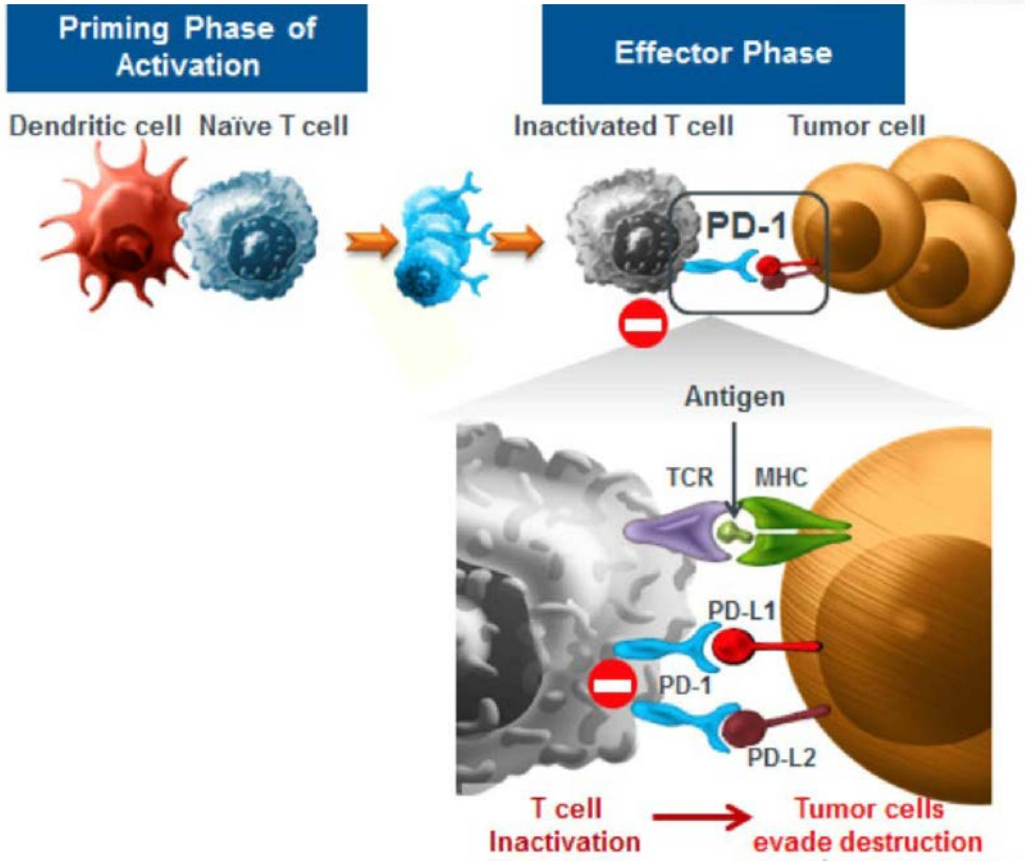
PD-L1 Blockade



- PD-1 is upregulated on activated T cells during the effector phase of the immune response
- PD-L1 and PD-L2 engage the PD-1 receptor on T cells to downregulate T-cell activity in the effector phase

Pardoll DM, Nat Rev Cancer 12:252, 2012

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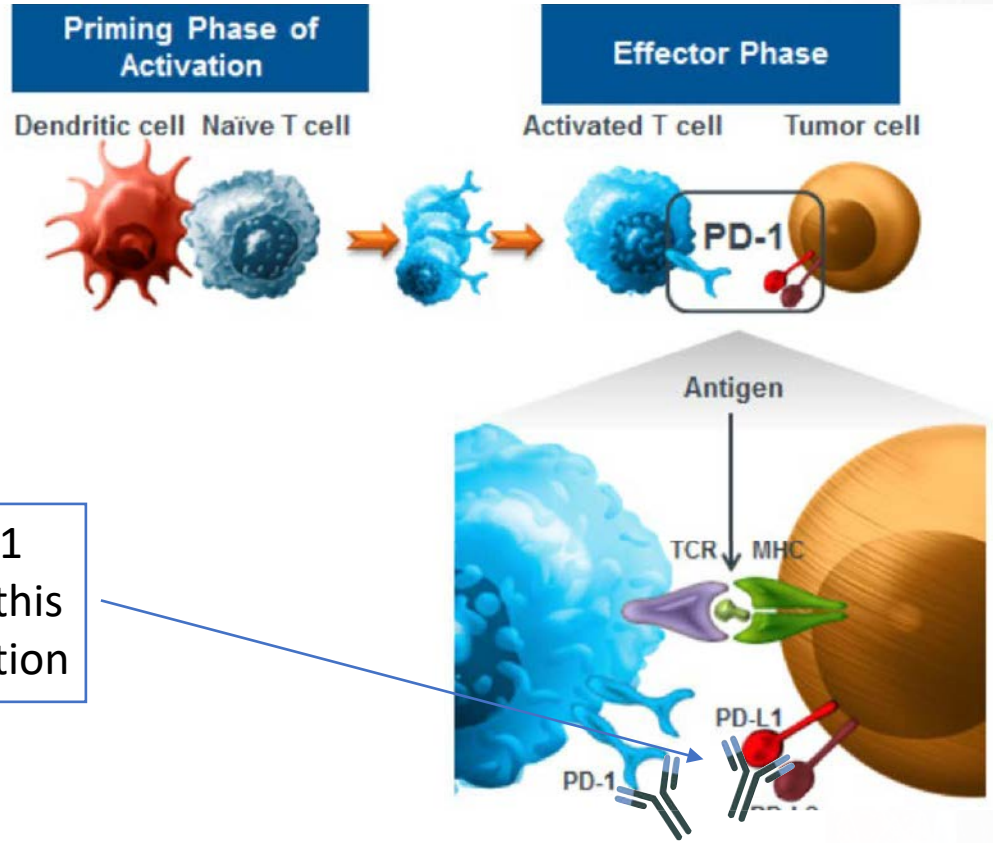
T-cell Activation and Tumor Kill



PD-1 and PD-L1 inhibitors block this signaling interaction

- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2

Pardoll DM, Nat Rev Cancer 12:252, 2012

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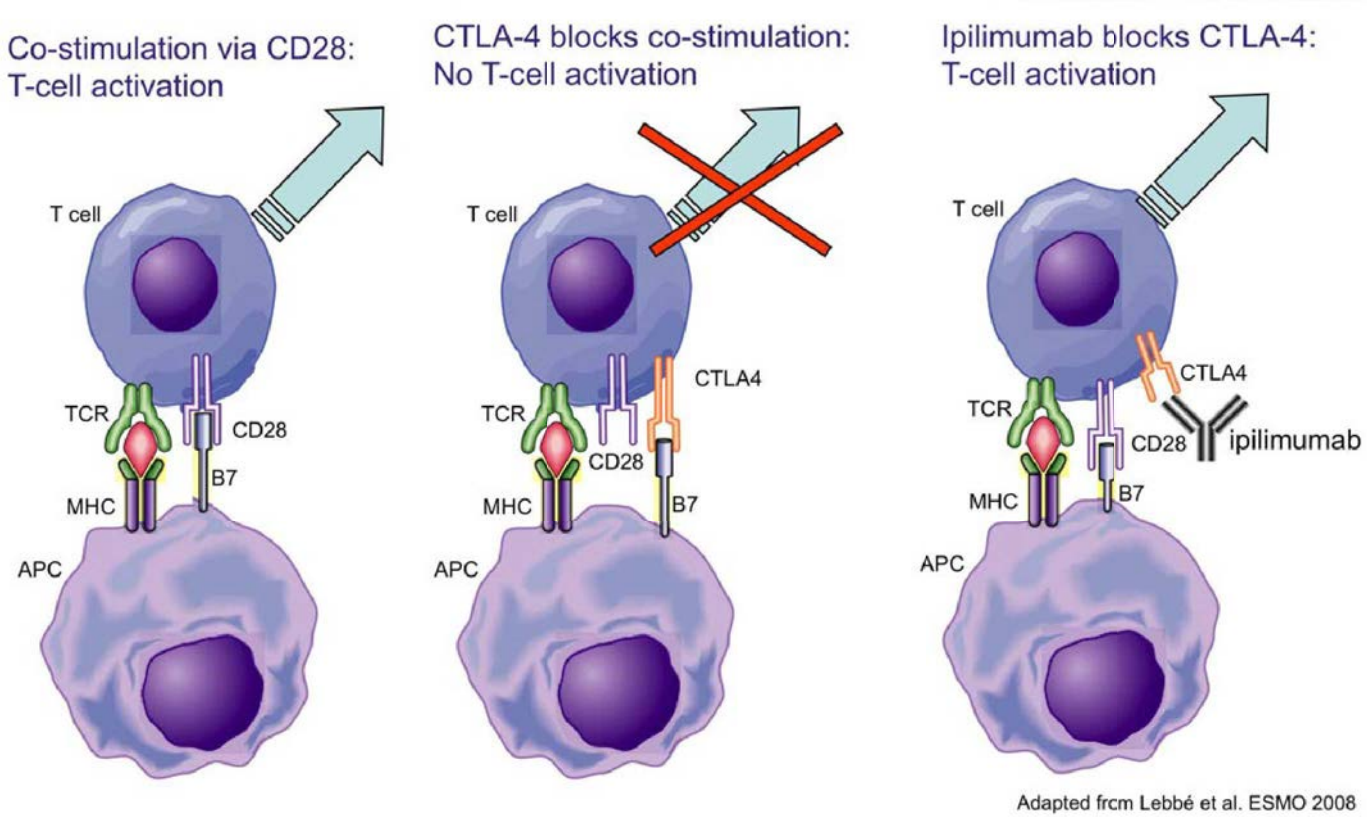
CTLA-4: A Brake on the Immune System



Adapted frcm Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

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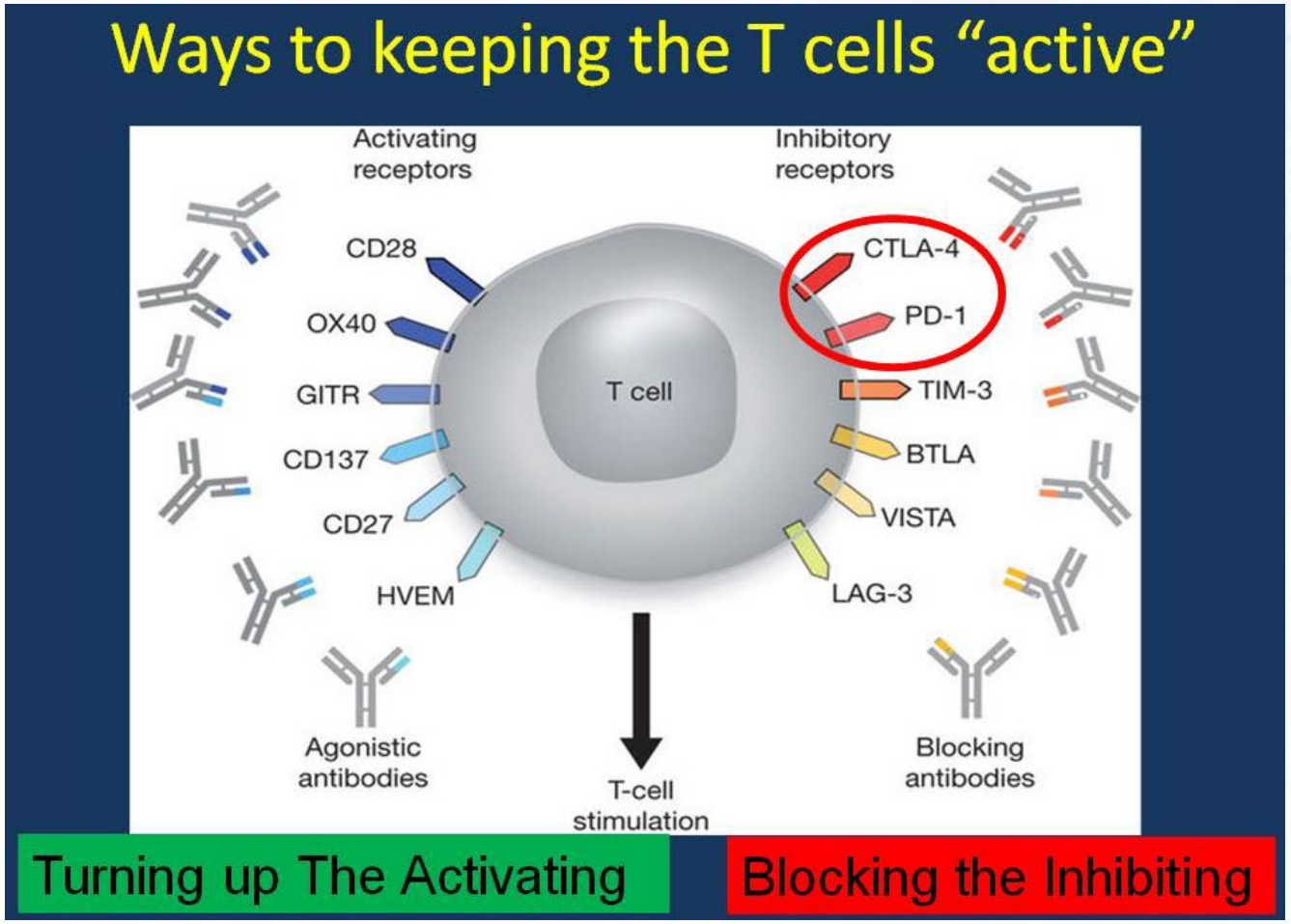
Immune Regulatory Signaling



Mellman, Nature 2011

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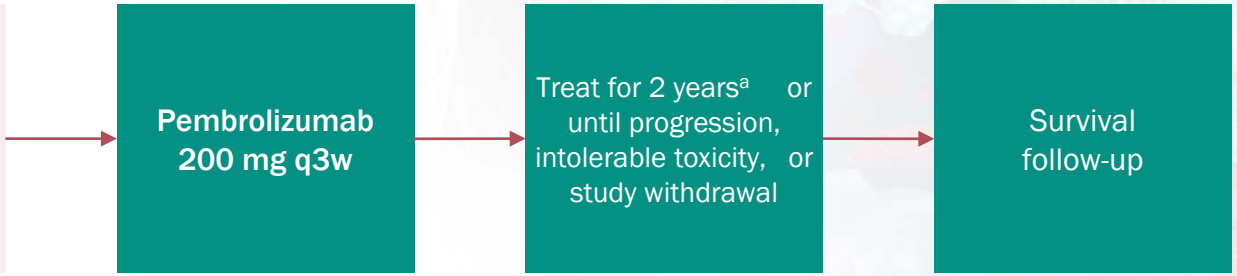
KEYNOTE 158: Phase 2 Trial of Pembrolizumab

Patients
- Age ≥18 years
- Histologically or cytologically confirmed advanced cervical cancer
- Progression on/intolerance to ≥1 line of standard therapy
- ECOG PS 0 or 1
- Tumor sample for biomarker analysis

Endpoints
- Primary: ORR
- Secondary: DOR, PFS, OS

Median follow-up: 36.9 months
Range: 34.3-41.0 months



Baseline characteristic		(N=98)
Age, median (range), y		46.0 (24-75)
ECOG PS 1, no. (%)		64 (65)
PD-L1+ tumor,[b] no. (%)		82 (84)
Prior therapies for recurrent/metastatic disease, no. (%)	1	44 (45)
	2	31 (32)
	3	13 (13)
	≥4	8 (8)

[a] Patients with stable disease or better when pembrolizumab was discontinued and subsequent progressive disease were eligible to resume pembrolizumab for up to 1 year.[b] CPS ≥1.

Chung HC, et al. SGO 2021. Abstract 41.

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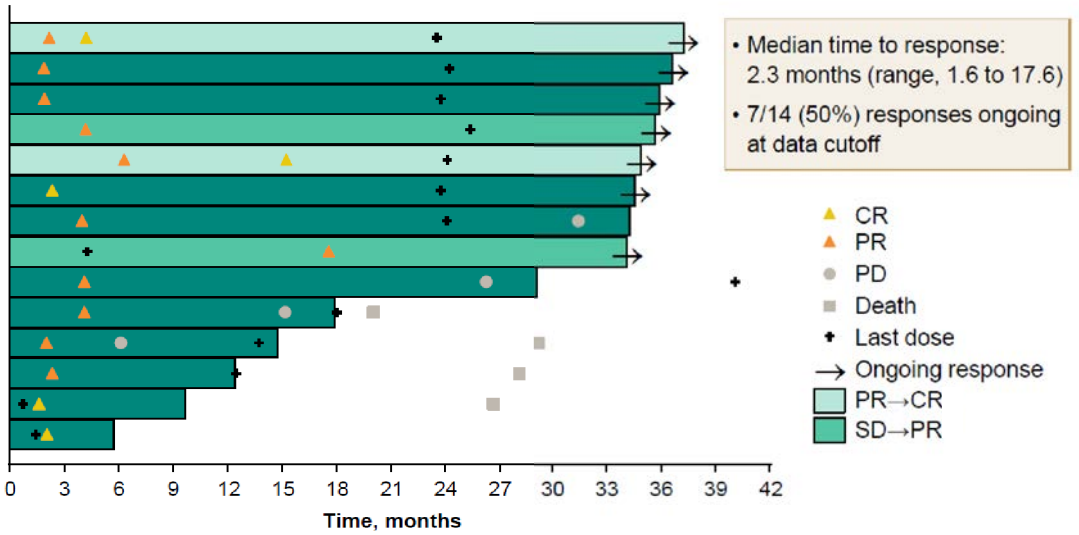
KEYNOTE 158: Safety and Efficacy

Outcome	Overall[a] (N=98)
ORR,[b] % (95% CI)	14.3 (8.0-22.8)
Best overall response, no. (%)	
CR	5 (5)
PR	9 (9)
SD	16 (16)
PD	55 (56)
Nonevaluable[c]	4 (4)
No assessment[d]	9 (9)

Safety summary

- 65% of patients experienced any TRAE
- 12% had grade ≥3 TRAEs
- 4% had TRAEs leading to discontinuation
- ~25% of patients had any irAE; ~4% were grade ≥3; 54% resolved
- 2% of patients discontinued pembrolizumab due to irAEs (hepatitis, n=2)

Time to and Duration of Response



Pembrolizumab received FDA approval for the treatment of PD-L1+ r/m cervical cancer; q6w dosing approved in April 2020

[a] Includes 1 patient with unknown PD-L1 expression level. [b] At the time of analysis, all responses were confirmed. [c] Target lesions not captured on ≥1 postbaseline imaging assessment. [d] Postbaseline tumor assessment not performed.

Chung HC, et al. SGO 2021. Abstract 41.

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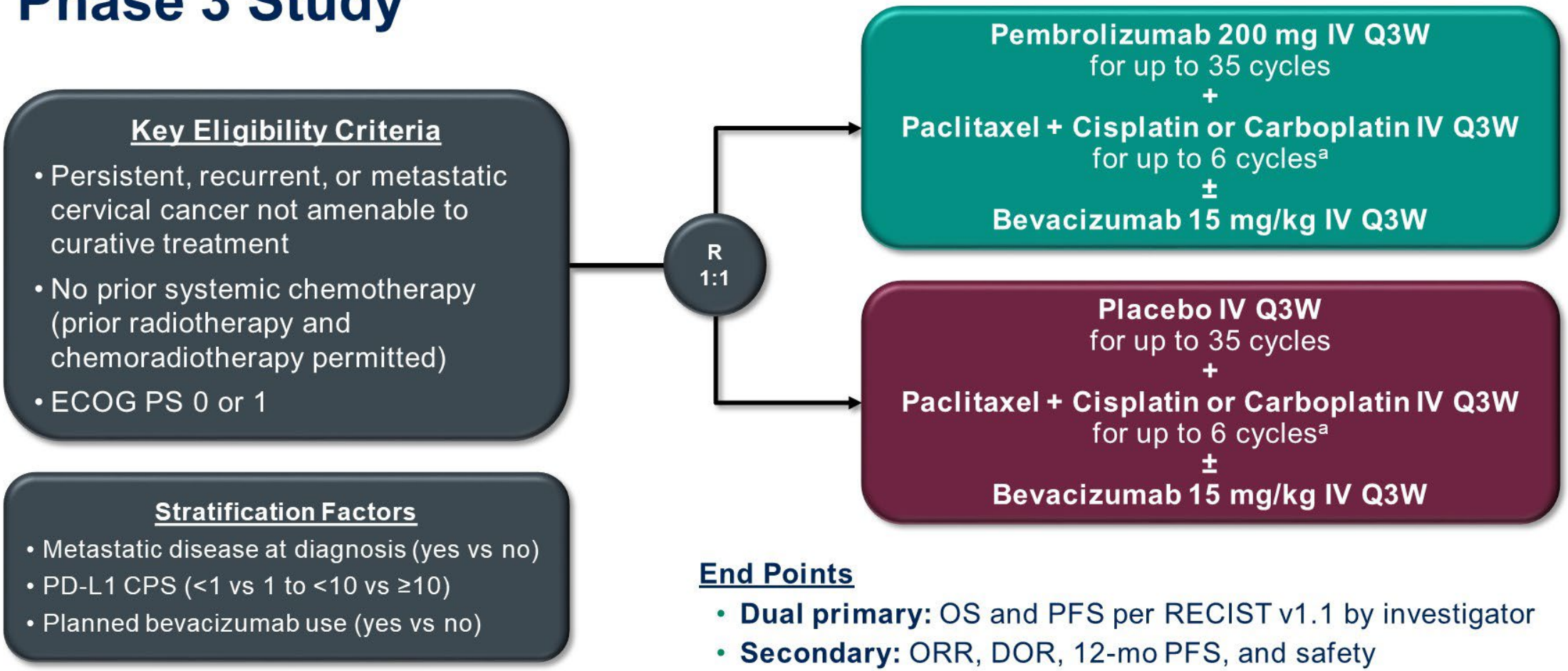
KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



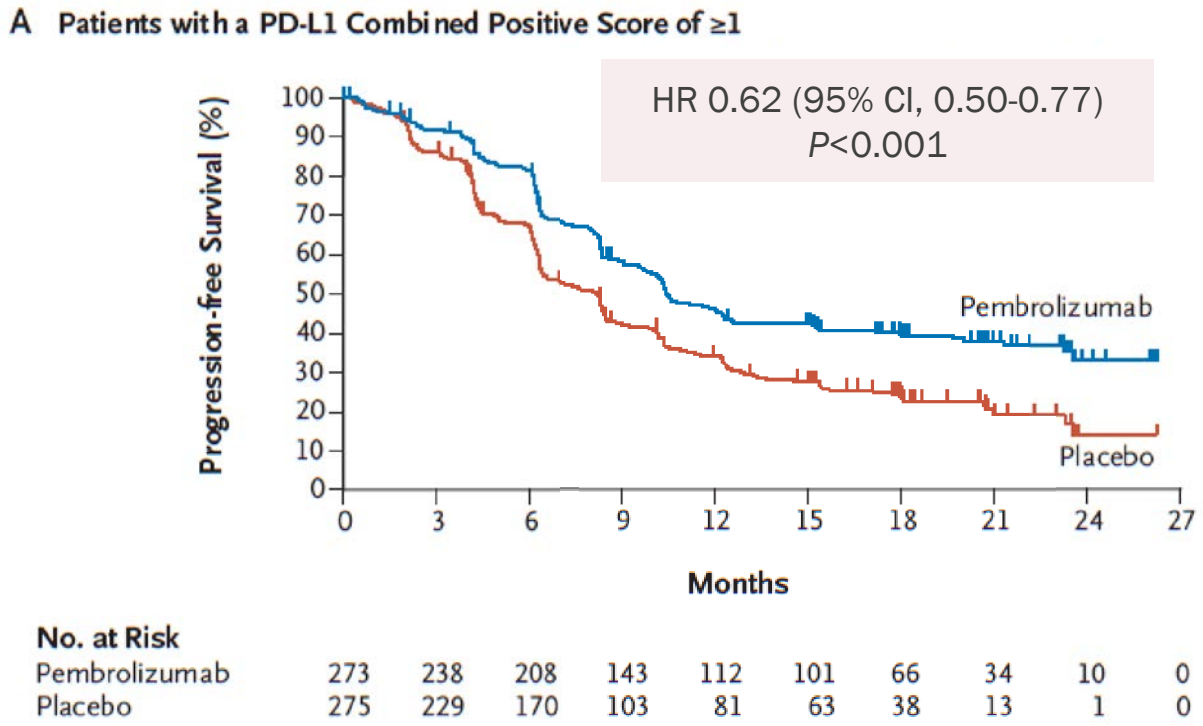
End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety

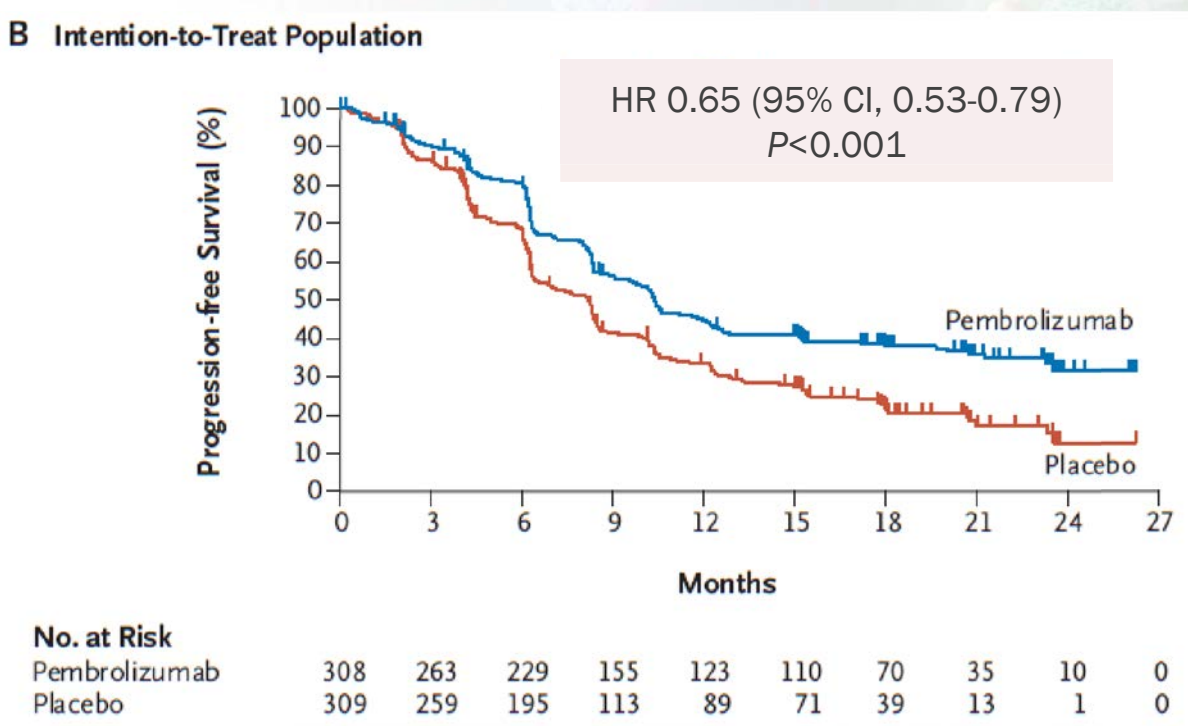
[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation. CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

KEYNOTE 826: PFS

PD-L1 CPS ≥1 Population



ITT Population



Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

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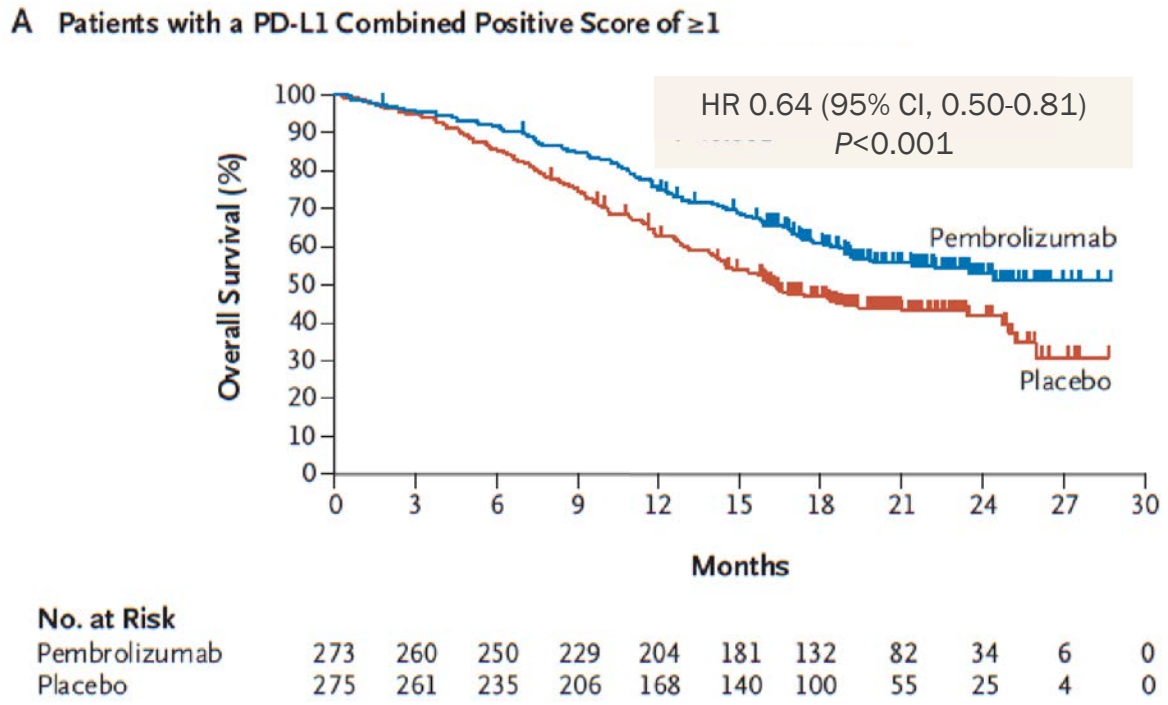
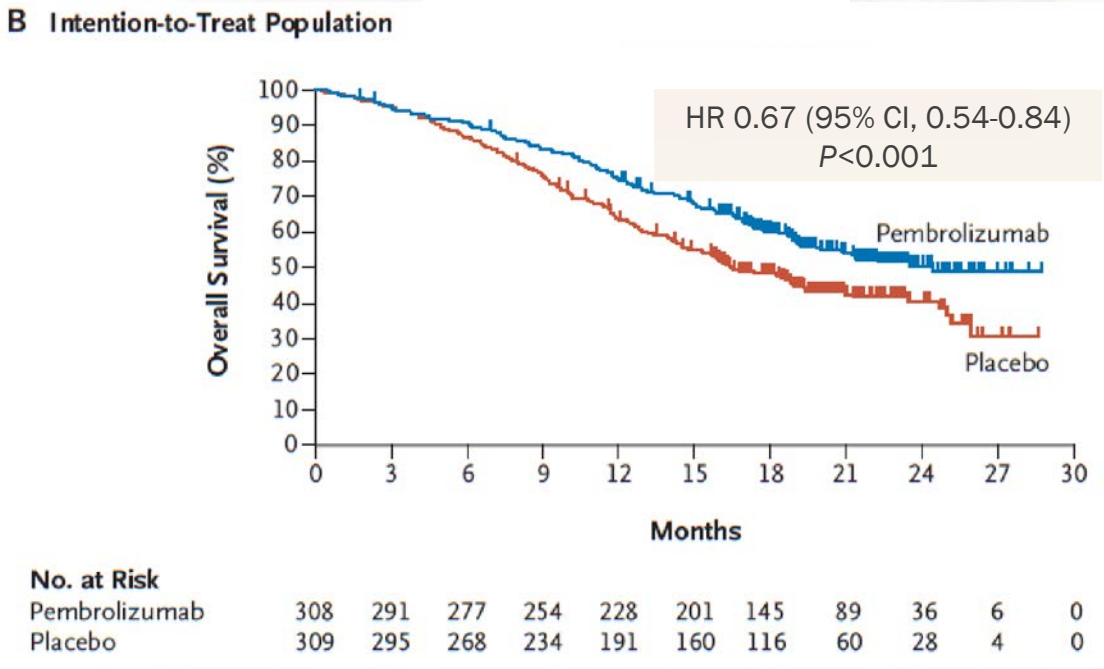
KEYNOTE 826: OS

PD-L1 CPS ≥1 Population



ITT Population



Pembrolizumab group mOS (ITT):
24.4 months

Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

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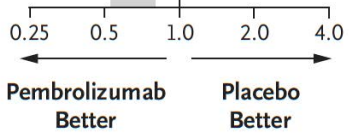
KEYNOTE 826: ITT Population Subgroup Analysis

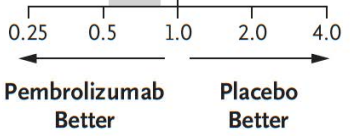
PFS

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	406/617	0.65 (0.53–0.79)
Age		
<65 yr	345/517	0.63 (0.50–0.78)
≥65 yr	61/100	0.77 (0.42–1.42)
Race		
White	239/360	0.70 (0.53–0.91)
Non-White	139/221	0.64 (0.45–0.90)
ECOG performance-status score		
0	197/348	0.65 (0.48–0.87)
1	207/267	0.69 (0.52–0.93)
PD-L1 combined positive score		
<1	51/69	0.94 (0.52–1.70)
1 to <10	152/231	0.68 (0.49–0.94)
≥10	203/317	0.58 (0.44–0.77)
Concomitant bevacizumab		
Yes	234/389	0.61 (0.47–0.79)
No	172/228	0.74 (0.54–1.01)
Metastatic disease at diagnosis		
Yes	137/190	0.92 (0.64–1.30)
No	269/427	0.58 (0.45–0.75)



OS

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	312/617	0.67 (0.54–0.84)
Age		
<65 yr	265/517	0.64 (0.50–0.82)
≥65 yr	47/100	0.88 (0.47–1.64)
Race		
White	189/360	0.68 (0.50–0.91)
Non-White	107/221	0.70 (0.47–1.04)
ECOG performance-status score		
0	141/348	0.68 (0.49–0.96)
1	169/267	0.68 (0.50–0.94)
PD-L1 combined positive score		
<1	40/69	1.00 (0.53–1.89)
1 to <10	118/231	0.67 (0.46–0.97)
≥10	154/317	0.61 (0.44–0.84)
Concomitant bevacizumab		
Yes	166/389	0.63 (0.47–0.87)
No	146/228	0.74 (0.53–1.04)
Metastatic disease at diagnosis		
Yes	104/190	0.84 (0.56–1.26)
No	208/427	0.61 (0.46–0.80)



Colombo N, et al. *N Engl J Med.* 2021;385(20):1856-1867.

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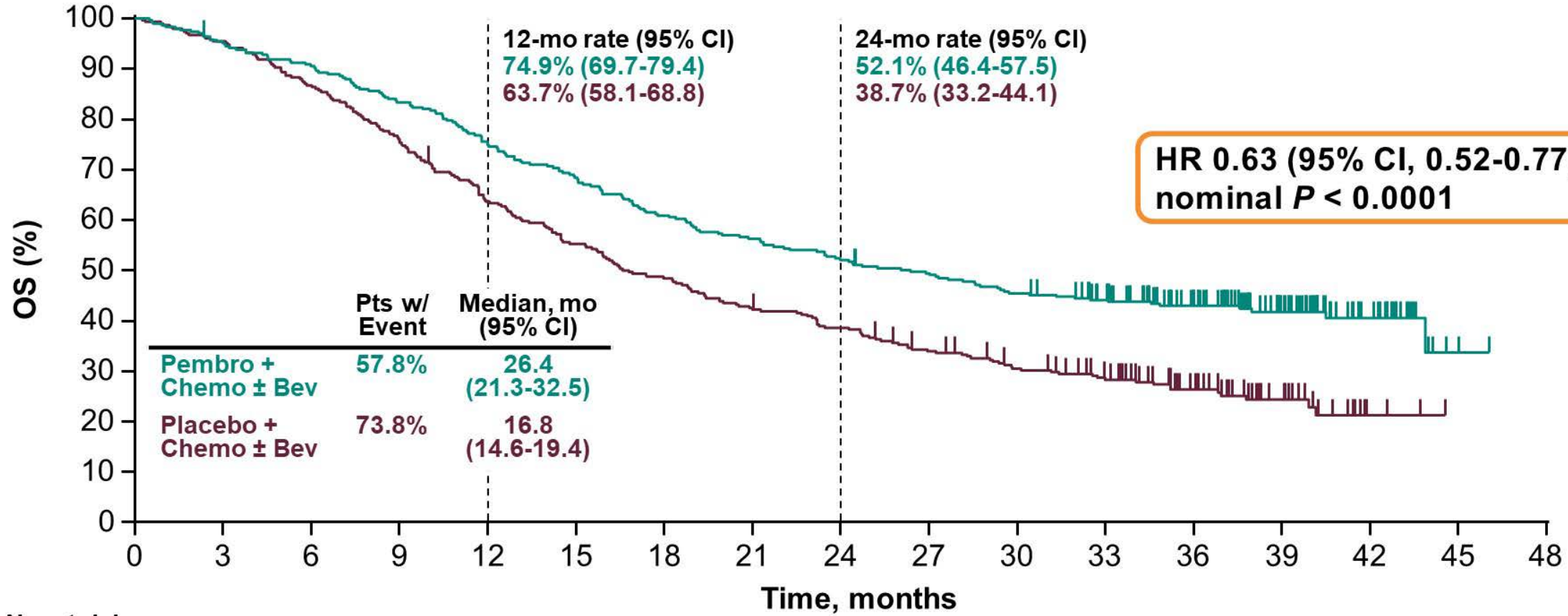
Protocol-Specified Final OS: All-Comer Population

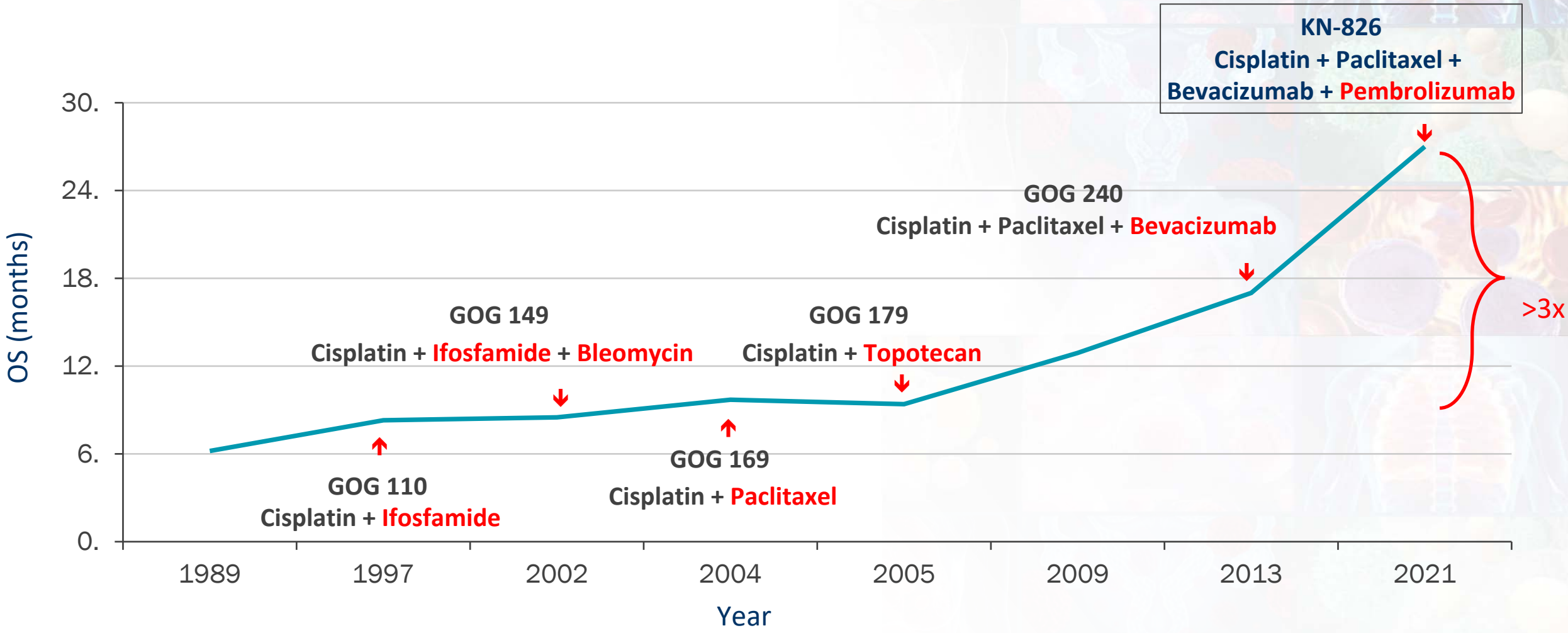


No. at risk

308	292	278	256	230	210	187	173	160	150	138	125	95	55	22	2	0
309	295	268	235	196	170	149	130	118	101	87	72	48	26	3	0	0

Data cutoff date: October 3, 2022.

Improving OS in Recurrent or Metastatic Cervical Cancer



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CheckMate 358: Phase 1/2 Trial of Nivolumab ± Ipilimumab

Key eligibility criteria
- Histologically confirmed squamous cell carcinoma of the cervix
- Recurrent/metastatic disease
- ≤2 prior therapies for recurrent/metastatic disease
- ECOG PS 0-1
- HPV: positive or unknown[a]

Treatment until disease progression, unacceptable toxicity, withdrawal of consent, or maximum of 24 months

Nivolumab (n=19)
Nivolumab 240 mg IV q2w

N3 + I1 (n=45)
Nivolumab 3 mg/kg q2w + Ipilimumab 1 mg/kg q6w

N1 + I3 (n=45)
Nivolumab 1 mg/kg q2w + Ipilimumab 3 mg/kg q3w x 4 cycles followed by nivolumab 240 mg q2w

+

N1 + I3 expansion arm[b]

First line: n=44
Second line: n=23

Primary endpoint: investigator-assessed ORR per RECIST v1.1
Secondary endpoints: DOR, Investigator assessed PFS, OS

	Nivolumab (n=19)	N3 + I1 (n=45)	N1 + I3 pooled (n=112)
Age, median (range), y	51 (28-75)	48 (32-76)	46 (24-77)
ECOG PS 1, no. (%)	8 (42)	22 (49)	60 (54)
Tumor PD-L1 expression, no. (%)			
<1%	7 (37)	15 (33)	36 (42)
≥1%	11 (58)	25 (56)	53 (47)
Not reported	1 (5)	5 (11)	23 (21)
Prior lines of systemic therapy in metastatic setting, no. (%)			
0	4 (21)	18 (40)	72 (64)
1	8 (42)	20 (44)	31 (28)
2	7 (37)	7 (16)	9 (8)

Nivolumab is not FDA approved for cervical cancer; it is in NCCN Guidelines® for patients whose cervical, vulvar, or vaginal tumors express PD-L1 (CPS ≥1)

[a] Patients with known HPV-negative tumors at study entry were not eligible. [b] Based on an early efficacy signal in the randomized N1+I3 arm, the study protocol was amended in July 2018 to include an N1+I3 expansion arm.

Naumann RW, *J Clin Oncol*. 2019;37(31):2825-2834.

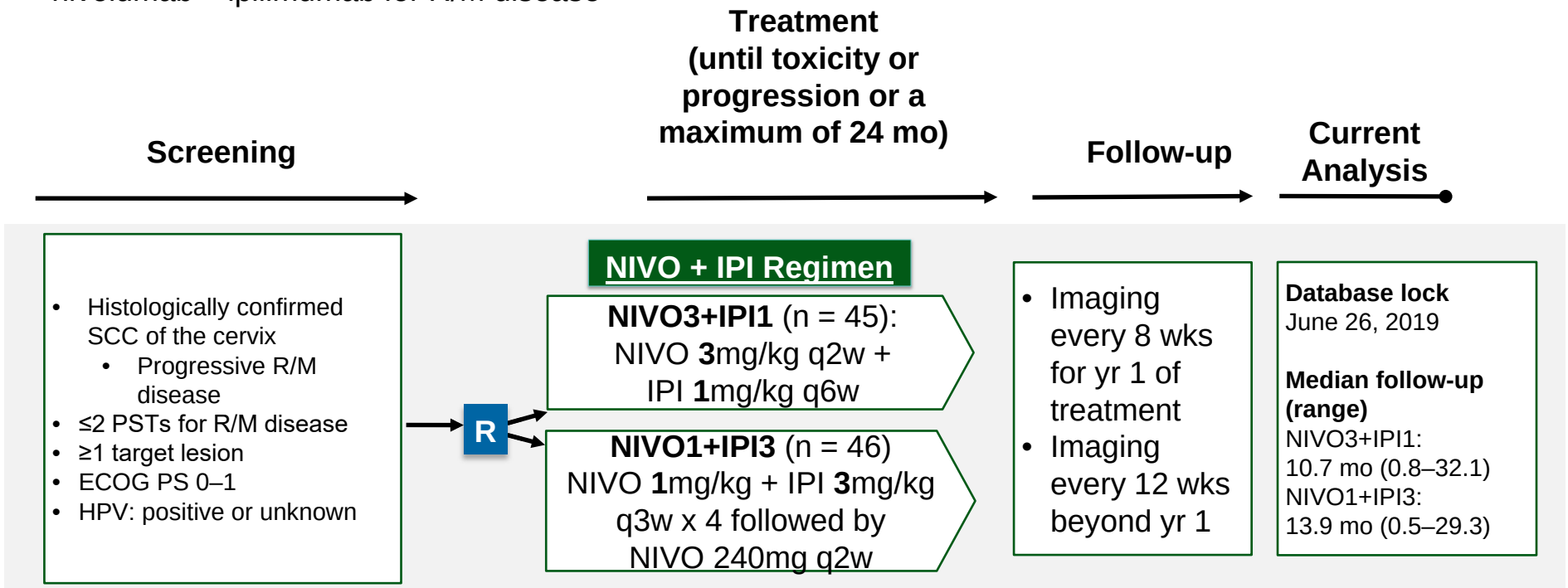
Nauman RW, ESMO 2019 LBA #5630

Oaknin A, ESMO 2022. Abstract 520MO.

Study Design and Current Analysis

CheckMate 358

Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease

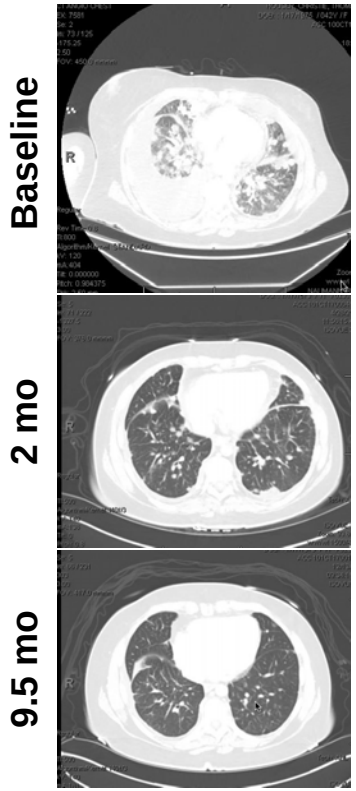


- **Study start date:** October 2015
- **Estimated completion date:** December 2019
- **Primary endpoint:** Investigator ORR by RECIST 1.1
- **Secondary endpoints:** OS, PFS, duration of response

Nauman RW, LBA #5630 ESMO 2019

Complete Response to Treatment
Nivolumab + Ipilimumab

CheckMate 358



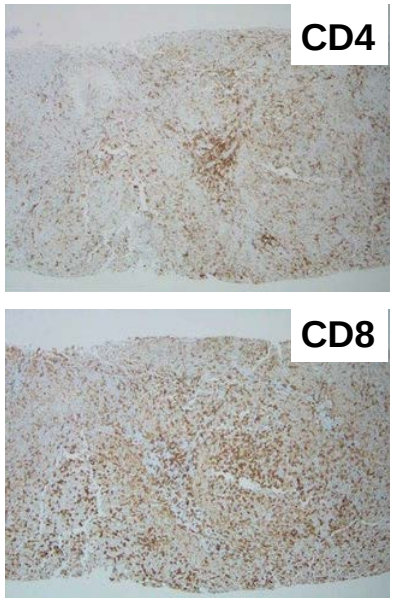
42y old woman with recurrent stage IIA (with lung metastases) HPV-positive SCC of the cervix; ECOG PS 1; tumor cell PD-L1 <1%

Before CheckMate 358

- First diagnosed with localized disease Jan-16
- Prior therapies
  - WPRT + cisplatin
  - HDRB, completed Apr-16
  - Carboplatin + paclitaxel + bevacizumab, completed Jan-17
    - Documented disease progression

CheckMate 358

- Treated with NIVO3+IPI1
- Complete response; time to response: 7.7 mo
- Biopsy at wk 7 showed only necrosis
- Stopped treatment after 2y
- No evidence of disease as of Aug-19 (7 mo post-treatment completion)
- NED as of Jan-24



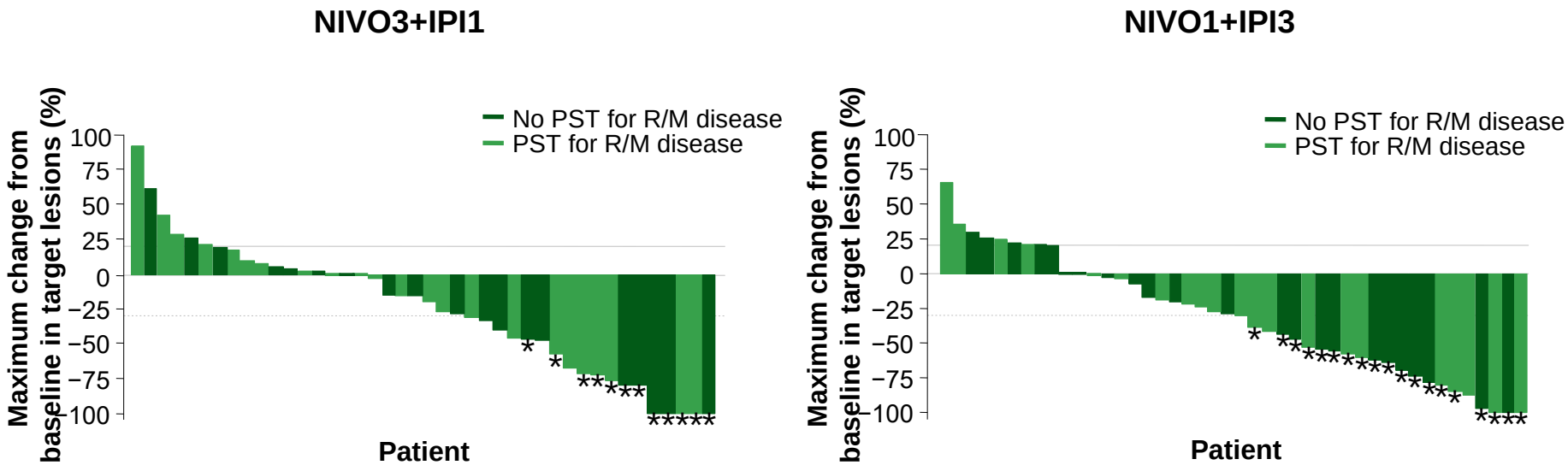
Biopsy (wk 7) showing extensive infiltration of CD8 cells with a high CD8/CD4 ratio

All images provided by Dr. Naumann, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA.
HDRB, high dose rate brachytherapy; SCC, squamous cell carcinoma, WPRT, whole pelvic radiotherapy.

Nauman RW, LBA #5630

Change From Baseline in Target Lesion Size

CheckMate 358



Bars with asterisks represent confirmed responses (complete or partial response).
PST, prior systemic therapy.

BARCELONA 2019 ESMO congress

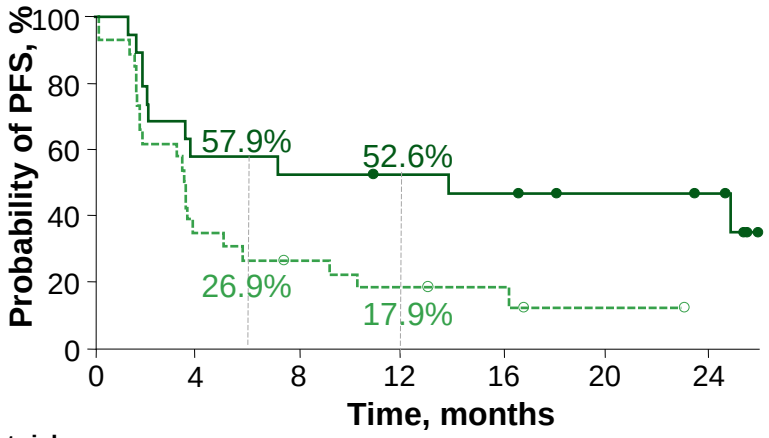
Nauman RW, LBA #5630

Progression-free Survival

CheckMate 358

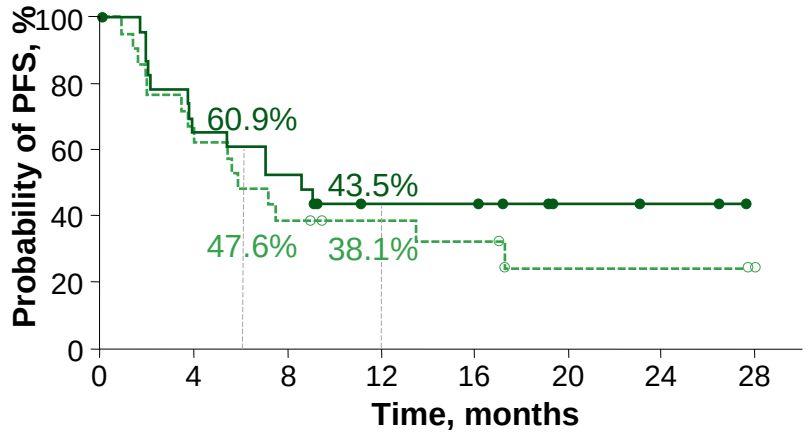
NIVO3+IPI1	
Median PFS, mo (95% CI)	
No PST for R/M disease	13.8 (2.1–NR)
PST for R/M disease	3.6 (1.9–5.1)

NIVO1+IPI3	
Median PFS, mo (95% CI)	
No PST for R/M disease	8.5 (3.7–NR)
PST for R/M disease	5.8 (3.5–17.2)



No. at risk

No PST	19	11	10	9	8	6	5
PST	26	9	6	4	3	1	0



No. at risk

No PST	24	15	12	7	7	3	2	0
PST	22	14	8	6	5	2	2	0

Owing to the high percentage of censored responses, median and rate estimators may be misleading. PST, prior systemic therapy.

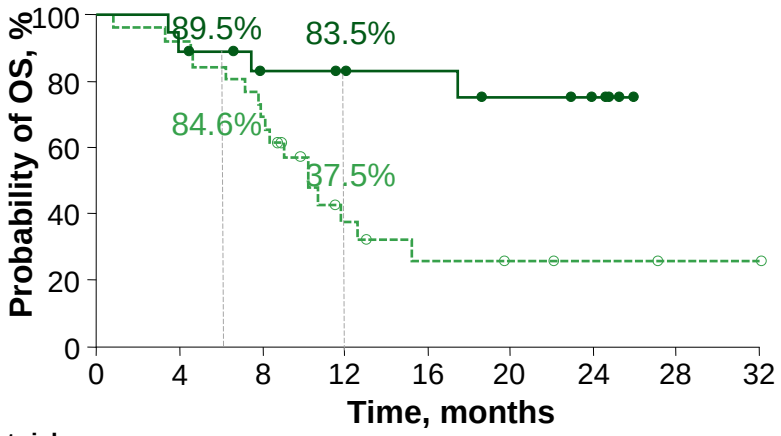
Nauman RW, LBA #5630

Overall Survival

CheckMate 358

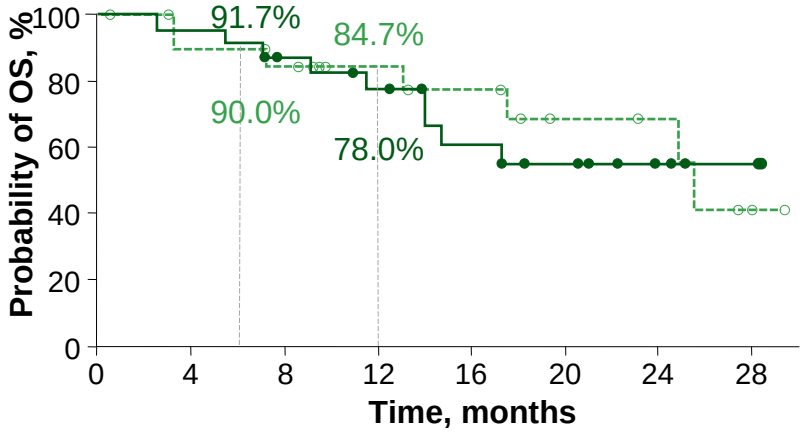
NIVO3+IPI1	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (17.4–NR)
PST for R/M disease	10.3 (7.9–15.2)

NIVO1+IPI3	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (13.9–NR)
PST for R/M disease	25.4 (17.5–NR)



No. at risk

No PST	19	17	13	12	11	9	6	0	0
PST	26	24	18	7	4	3	2	1	1



No. at risk

No PST	24	23	19	16	11	8	4	2
PST	22	18	16	12	10	6	5	1

Owing to the high percentage of censored responses, median and rate estimators may be misleading. NR, not reached; PST, prior systemic therapy.

Nauman RW, LBA #5630

Tumor Response

	NIVO3+IPI1		NIVO1+IPI3	
Response	**No PST for R/M disease, n = 19**	**PST for R/M disease, n = 26**	**No PST for R/M disease n = 24**	**PST for R/M disease, n = 22**
ORR, % (95% CI)	31.6 (12.6–56.6)	23.1 (9.0–43.6)	45.8 (25.6–67.2)	36.4 (17.2–59.3)
Best overall response†				
Complete response	3 (15.8)	1 (3.8)	1 (4.2)	3 (13.6)
Partial response	3 (15.8)	5 (19.2)	10 (41.7)	5 (22.7)
Stable disease	6 (31.6)	8 (30.8)	6 (25.0)	8 (36.4)
Progressive disease	7 (36.8)	11 (42.3)	6 (25.0)	5 (22.7)
Duration of response, median, mo (95% CI)	NR (6.6–NR)	14.6 (7.5–NR)	NR (4.6–NR)	9.5 (1.9–NR)
ORR by tumor cell PD-L1 expression,‡				
PD-L1 ≥1%, # responders/# treated (%) [95% CI]	30.4%			
PD-L1 <1%, # responders/# treated (%) [95% CI]	24.0%			

Summary of TRAEs

CheckMate 358

Event, n (%)	NIVO3+IPI1 (n=45)		NIVO1+IPI3 (n=46)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs	36 (80.0)	13 (28.9)	38 (82.6)	17 (37.0)
Treatment-related SAEs	12 (26.7)	8 (17.8)	16 (34.8)	10 (21.7)
TRAEs leading to treatment discontinuation	6 (13.3)	2 (4.4)	9 (19.6)	6 (13.0)
Treatment-related SAEs leading to treatment discontinuation	2 (4.4)	1 (2.2)	5 (10.9)	5 (10.9)

- No new safety signals
- Higher incidence of TRAEs and treatment-related SAEs leading to treatment discontinuation in NIVO1+IPI3 compared with NIVO3+IPI1
- No treatment-related deaths

SAE, serious adverse event; TRAE, treatment-related adverse event

Nauman RW, LBA #5630

CheckMate 358: Safety

No. of patients, n (%)	Nivolumab (n=19)		N3 + I1 (n=45)		N1 + I3 pooled (n=112)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE	12 (63)	4 (21)	36 (80)	13 (29)	99 (88)	52 (46)
TRAEs leading to discontinuation	2 (11)	1 (5)	8 (18)	4 (9)	27 (24)	21 (19)
Serious TRAEs	3 (16)	3 (16)	12 (27)	8 (18)	47 (42)	34 (30)
IMAE[a,b]						
Endocrine						
Hypothyroidism/thyroiditis	1 (5)	0	11 (24)	1 (2)	27 (24)	0
Hyperthyroidism	0	0	5 (11)	1 (2)	15 (13)	1 (1)
Diabetes mellitus	0	0	2 (4)	1 (2)	0	0
Hypophysitis	0	0	1 (2)	0	5 (4)	1 (1)
Adrenal insufficiency	0	0	1 (2)	0	1 (1)	0
Nonendocrine						
Pneumonitis	1 (5)	1 (5)	1 (2)	0	12 (11)	4 (4)
Rash	0	0	4 (9)	0	17 (15)	4 (4)
Hepatitis	0	0	3 (7)	3 (7)	20 (18)	18 (16)
Diarrhea/colitis	0	0	2 (4)	1 (2)	18 (16)	6 (5)
Nephritis and renal dysfunction	0	0	1 (2)	1 (2)	2 (2)	1 (1)
Hypersensitivity	0	0	0	0	1 (1)	1 (1)
Treatment-related deaths, n	0		0		1[c]	

Naumann RW, *J Clin Oncol*. 2019;37(31):2825-2834.

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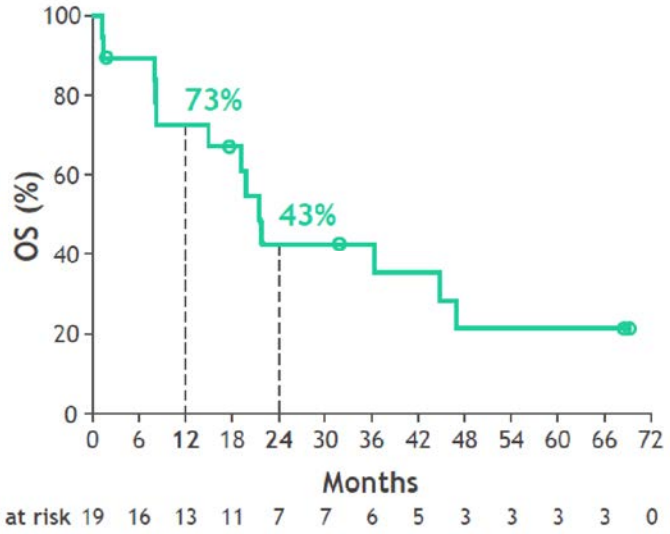
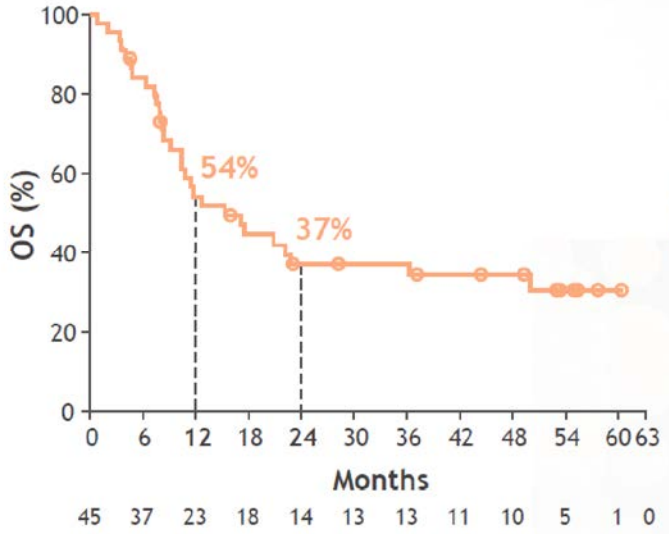
CheckMate 358: OS and PFS

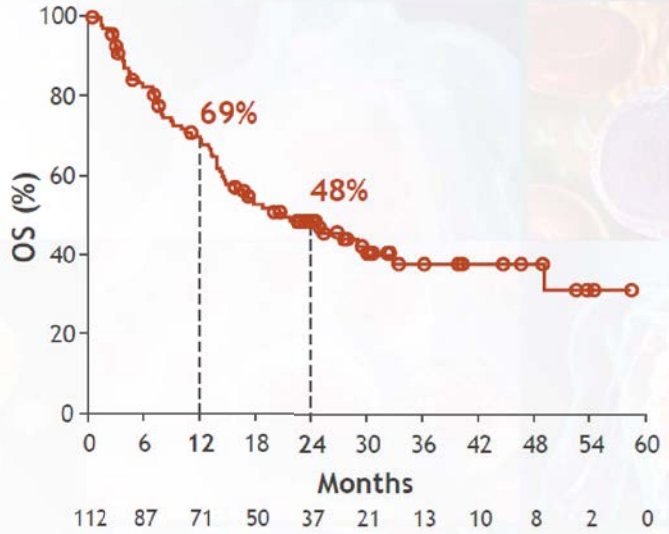
	NIVO (n = 19)
Median OS, mo (95% CI)	21.6 (8.3-46.9)
12-month OS, % (95% CI)	73 (46-88)
24-month OS, % (95% CI)	43 (20-64)



	N3+I1 (randomized) (n = 45)
Median OS, mo (95% CI)	15.2 (9.0-36.2)
12-month OS, % (95% CI)	54 (38-68)
24-month OS, % (95% CI)	37 (23-51)



	N1+I3 pooled (randomized + expansion) (n = 112)
Median OS, mo (95% CI)	20.9 (14.4-32.8)
12-month OS, % (95% CI)	69 (60-77)
24-month OS, % (95% CI)	48 (38-57)



- Median PFS (investigator-assessed) was 5.1 (95% CI, 1.9-9.1), 3.8 (95% CI, 2.1-10.3), and 5.8 (95% CI, 3.8-9.3) months for the nivolumab, N3+I1, and N1+I3 arms, respectively

[a]The minimum follow-up for OS was 67.4, 36.9, and 17.9 months for the nivolumab, N3+I1, and N1+I3 arms.

Oaknin A, et al. ESMO 2022. Abstract 520MO.

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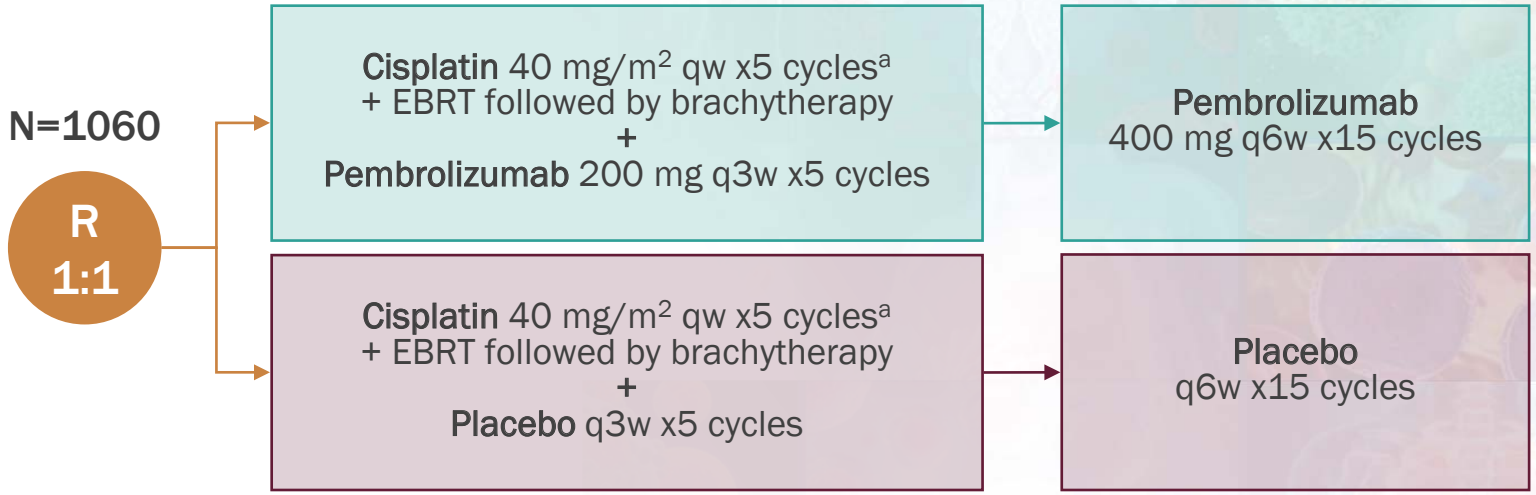
KEYNOTE-A18: Phase 3 Trial of Pembrolizumab + Chemoradiotherapy for High-Risk Locally Advanced Cervical Cancer

- FIGO 2014 stage IB2-IIB (node-positive) or stage III-IVA (node-positive or node-negative)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve



- Stratification factors: planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT), stage at screening (stage IB2-IIB vs III-IVA), and planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQ2D])

Endpoints
- Primary: PFS and OS
- Key secondary: 24-mo PFS, ORR, PROs, and safety

[a] A sixth cycle was allowed per investigator discretion.

Lorusso D, et al. ESMO 2023. Abstract LBA38.

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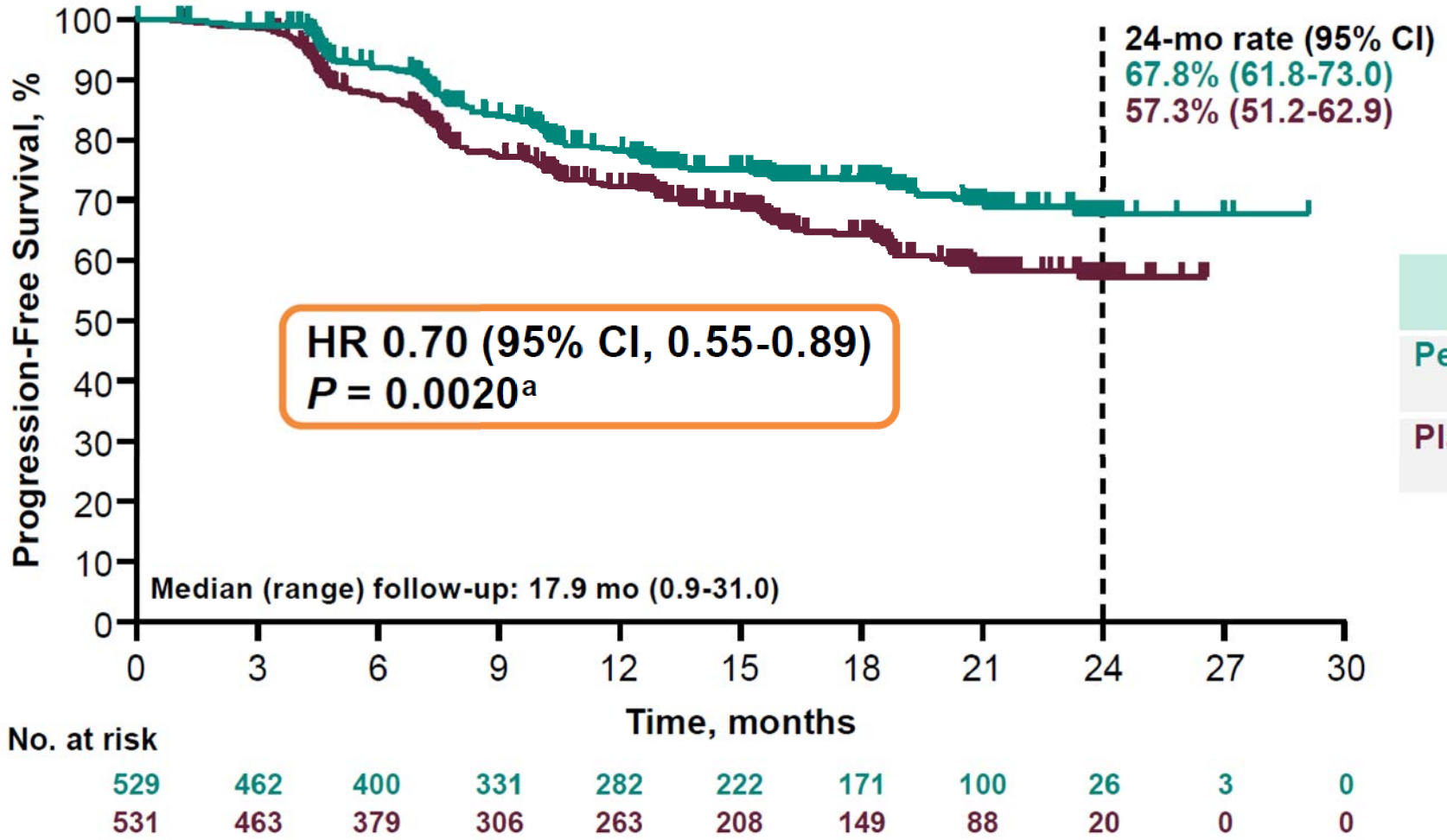
KEYNOTE-A18: PFS



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

Lorusso D, et al. ESMO 2023. Abstract LBA38.

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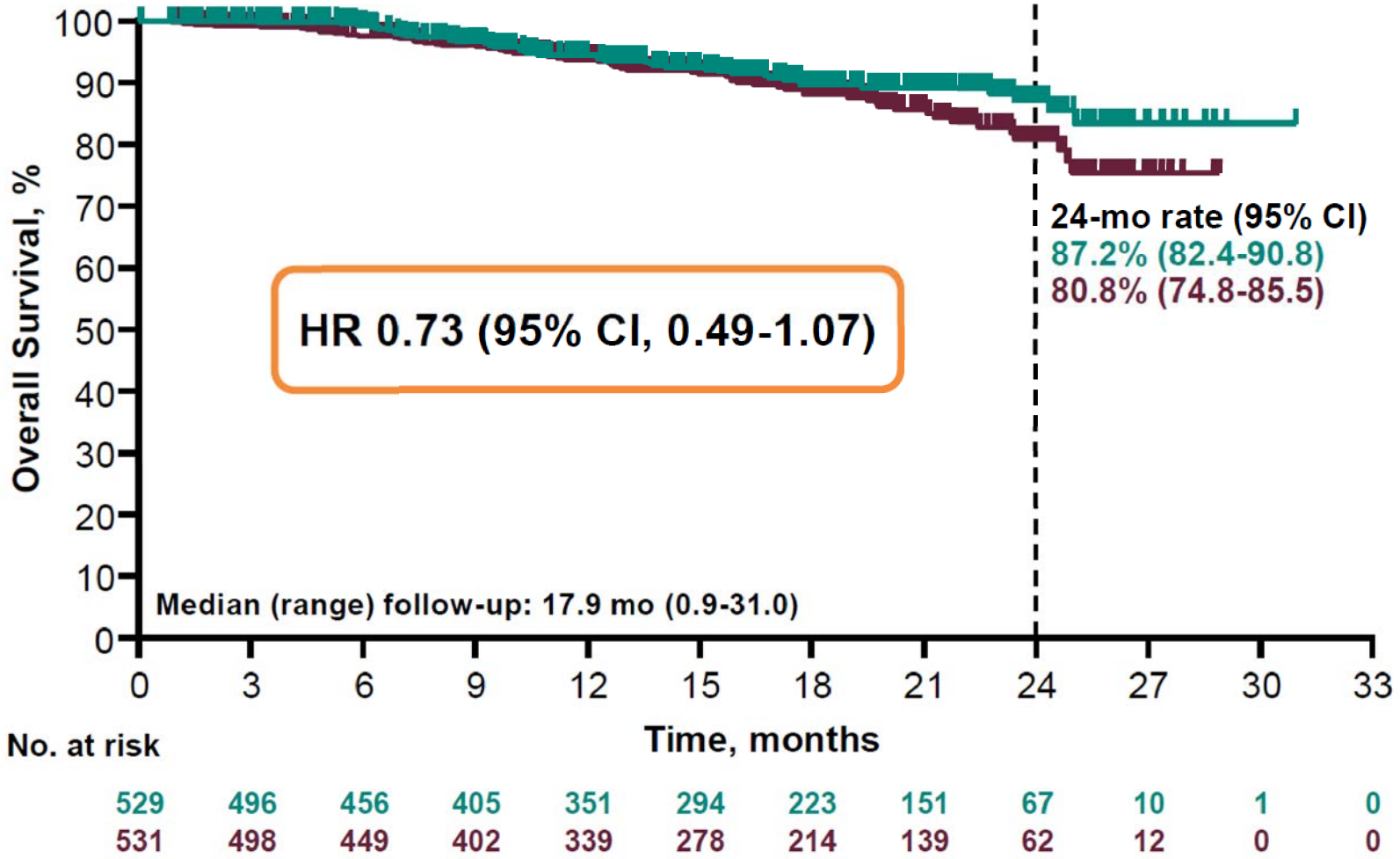
KEYNOTE-A18: OS



	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction[a]

Lorusso D, et al. ESMO 2023. Abstract LBA38.

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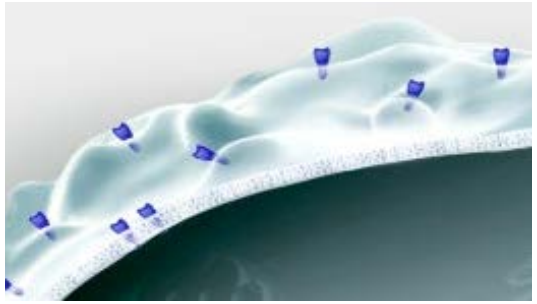
Tisotumab Vedotin



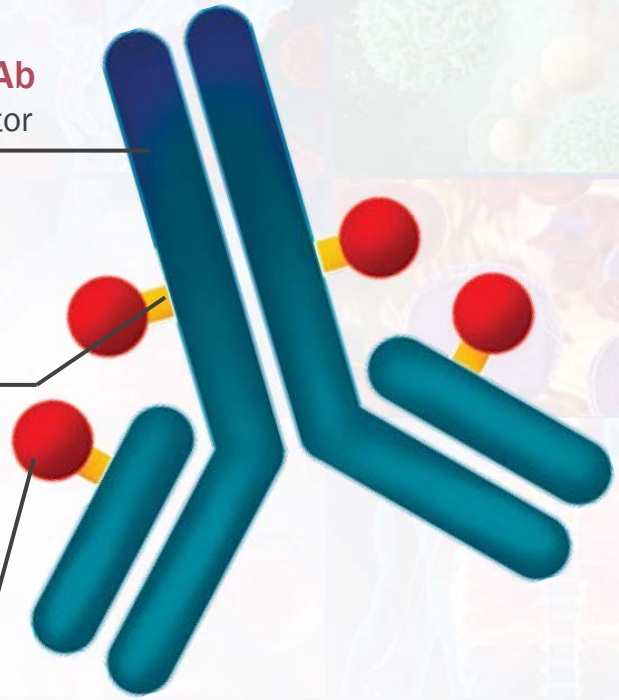
Tissue factor (TF)

- Transmembrane protein: main physiological initiator of coagulation[1]
  - Role in oncogenesis includes angiogenesis, cell adhesion, motility, and cell survival[2]
- Highly expressed in many solid tumors including cervical, ovarian, pancreatic, SCCHN, NSCLC, and others[3-7]
- Expression associated with poor clinical outcomes, tumor initiation, progression, angiogenesis, and metastasis[2]

Fully human mAb
Targets tissue factor

Linker
Protease-cleavable val-citrulline maleimidocaproyl linker
Conjugated to monoclonal antibody via cysteine residues

Cytotoxic payload
Monomethyl auristatin E (MMAE), a microtubule-disrupting agent
Drug-to-antibody ratio of approximately 4:1



The human anti-TF antibody of tisotumab vedotin inhibits tumor proliferation pathways with minimal impact on clotting cascade

Coleman R, et al. ESMO 2020. Abstract LBA32.

1. Versteeg HH, et al. *Semin Thromb Hemost*. 2015;41(7):747-755. 2. van den Berg YW, et al. *Blood*. 2012;119(4):924-932. 3. Chu AJ. *Int J Inflam*. 2011;2011:367284. 4. Forster Y, et al. *Clin Chim Acta*. 2006;364(1-2):12-21. 5. Cocco E, et al. *BMC Cancer*. 2011;11:263. 6. Ruf W, et al. *J Thromb Haemost*. 2011;9(suppl 1):306-315. 7. Jacobs, et al. *J Clin Oncol*. 2012;30(15_suppl; abstr e16022).

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InnovaTV 204/GOG-3023/ENGOT-cx6: Phase 2 Global Trial of Tisotumab Vedotin

Key eligibility criteria

- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] plus bevacizumab (if eligible)
- Received 1 or 2 previous systemic regimens[b]
- ECOG PS 0-1

Tisotumab vedotin
2.0 mg/kg IV q3w

Enrolled: 102[c]
Treated: 101[d]

Until PD or unacceptable toxicity

Primary endpoint

- ORR per RECIST v1.1, assessed by radiographic review by IRC

Secondary endpoints

- ORR, DOR, TTR, and PFS
- OS
- Safety

Exploratory endpoints

- Biomarkers
- HRQOL

Tumor responses assessed using CT or MRI at baseline every 6 weeks for the first 30 weeks and every 12 weeks thereafter

FDA approved September 2021 for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy

[a] Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b] Adjuvant or neoadjuvant chemotherapy, or if administered with radiation therapy, was not counted as a previous systemic regimen. [c] June 2018 to April 2019. [d] Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin, and to provide ≥80% power to exclude an ORR of up to ≤11%.

Coleman R, et al. *Lancet Oncol.* 2021;22(5):609-619.

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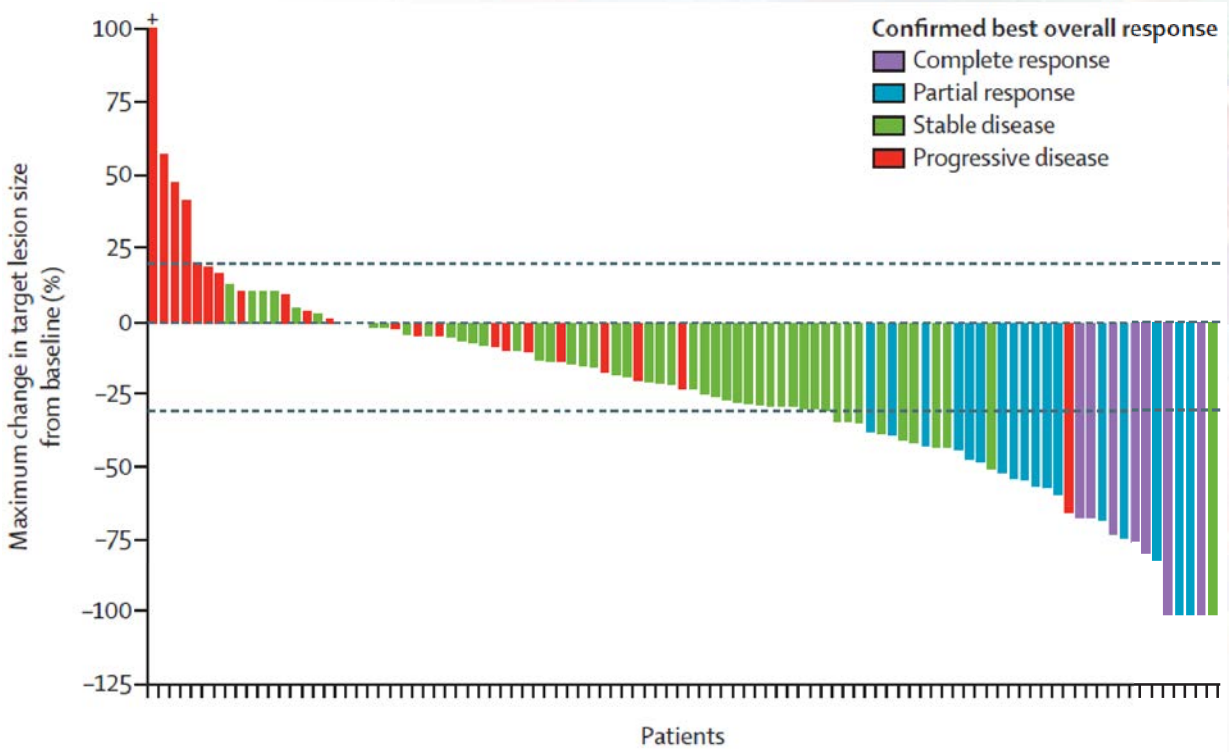
InnovaTV 204: Antitumor Activity by IRC Assessment

Response rates by IRC assessment	(N=101)
ORR[a] (95% CI), %	24 (16-33)
CR, no. (%)	7 (7)
PR, no. (%)	17 (17)
SD, no. (%)	49 (49)
PD, no. (%)	24 (24)
Not evaluable, no. (%)	4 (4)
Disease control rate[b] (95% CI), %	72 (63-81)
Median DOR (95% CI), mo	8.3 (4.2-NR)
Median time to response (IQR), mo	1.4 (1.3-1.5)
Median PFS (95% CI), mo	4.2 (3.0-4.4)

Target lesions reduced in 79% of patients with ≥1 postbaseline scan[c]



Median follow-up: 10.0 months.

[a] Based on the Clopper-Pearson method. [b] Disease control rate is the proportion of patients with a confirmed CR, PR, or SD.

[c] Percent changes greater than 100% were truncated at 100% (indicated by the + symbol).

Coleman R, et al. *Lancet Oncol.* 2021;22(5):609-619.

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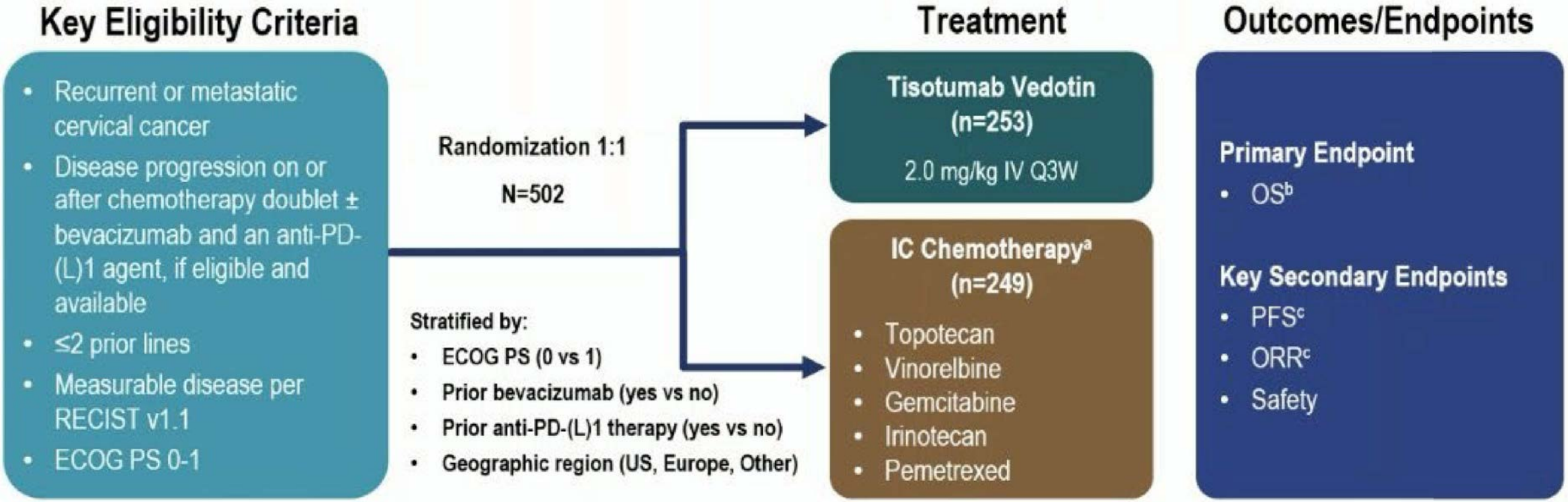
innovaTV 301: A Randomized, Open-Label, Phase 3 Trial



- Data presented herein are a planned interim analysis

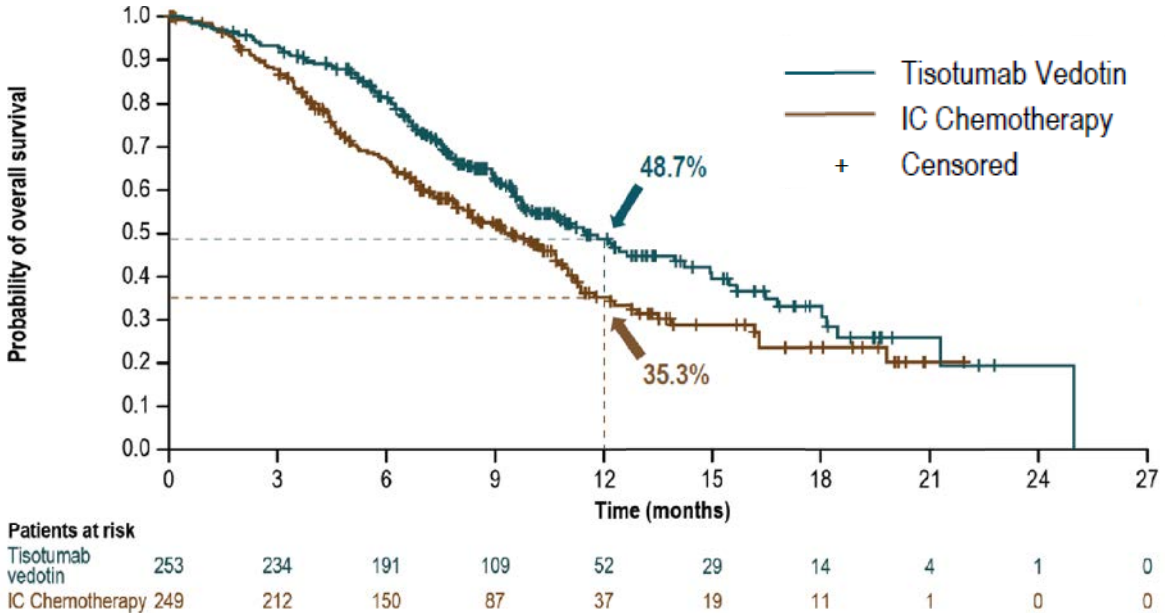
IC, investigator's choice

End of treatment visit occurred 30 days after the last dose of treatment. Survival follow-up occurred every 60 days after the last dose of treatment.

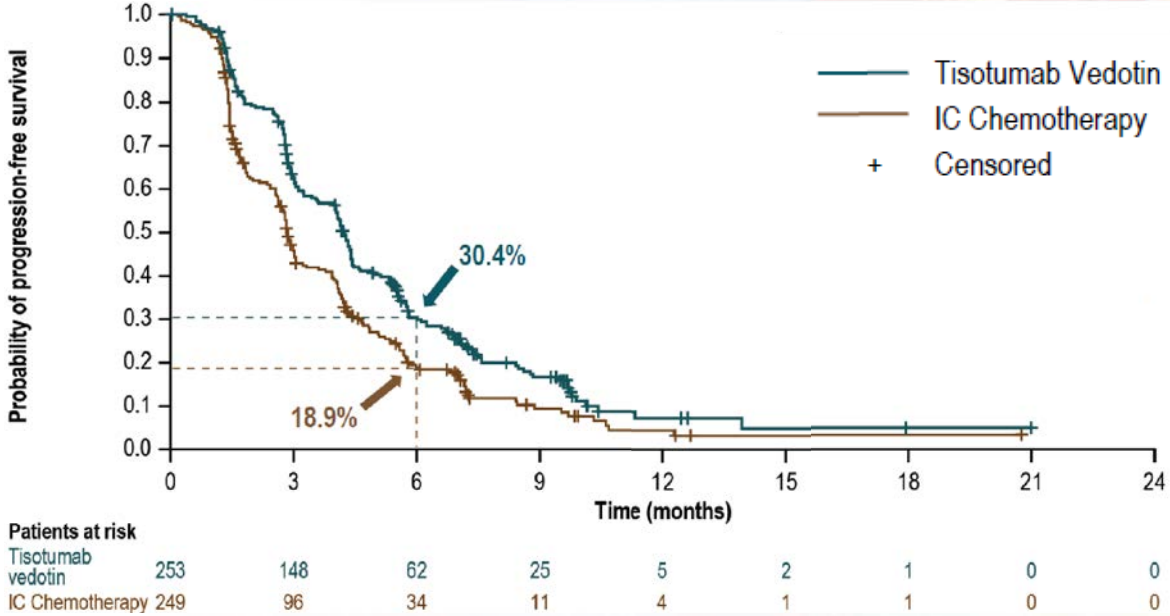
[a]Chemotherapy regimens were given at the following doses: topotecan: 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days; vinorelbine: 30 mg/m^2 IV on Days 1 and 8, every 21 days; gemcitabine: 1000 mg/m^2 IV on Days 1 and 8, every 21 days; irinotecan: 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days; pemetrexed: 500 mg/m^2 on Day 1, every 21 days; [b]OS was defined as the time from the date of randomization to the date of death due to any cause; [c]Assessed by investigator.

InnovaTV 301: OS and PFS

	Events/ Total	mOS (95% CI)	HR (95% CI)	Stratified log-rank P value[a]
TV	123/253	**11.5** (9.8-14.9)	**0.70** (0.54-0.89)	0.0038
Chemo	140/249	**9.5** (7.9-10.7)		



	Events/ Total	mPFS (95% CI)	HR (95% CI)	Stratified log-rank P value[b]
TV	198/253	**4.2** (4.0-4.4)	**0.67** (0.54-0.82)	<0.0001
Chemo	194/249	**2.9** (2.6-3.1)		



[a] The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

[b] The threshold for statistical significance is 0.0453 (2-sided), based on the actual number of PFS events at interim analysis.

Vergote I, et al. ESMO 2023. Abstract LBA9.

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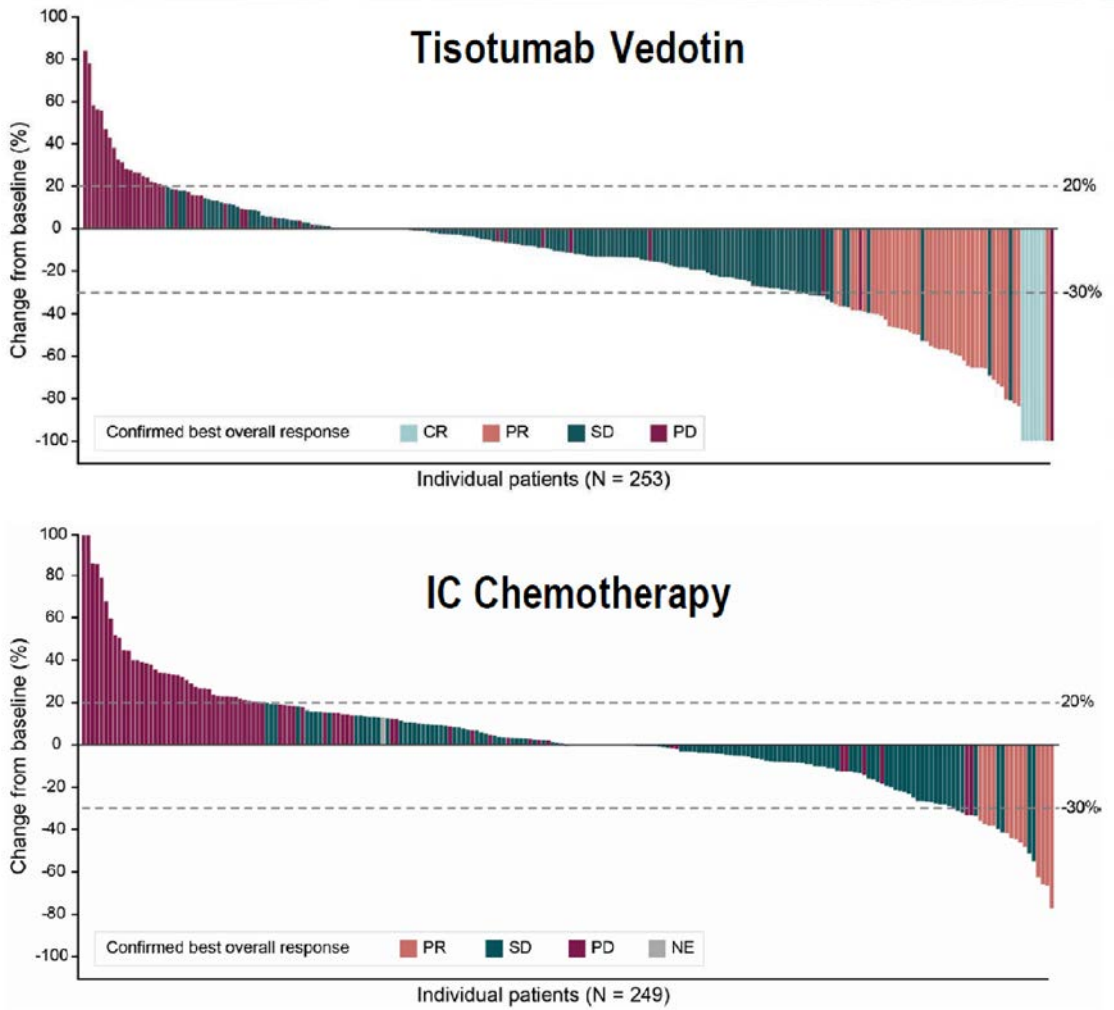
InnovaTV 301: Antitumor Activity

	TV (N=253)	Chemo (N=249)
ORR, % (95% CI)	**17.8** (13.3-23.1)	**5.2** (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	<0.0001	
Best overall response, no. (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Not evaluable	15 (5.9)	30 (12.0)
DCR[a], % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
mDOR (95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)



[a] DCR defined as CR+PR+SD; CR and PR were confirmed responses. The minimum criteria for SD duration was ≥5 weeks after the date of randomization.

Vergote I, et al. ESMO 2023. Abstract LBA9.

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InnovaTV 205/ENGOT-cx8/GOG-3024

Phase 1b/2 Study of TV Monotherapy or in Combination With Other Anti-Cancer Agents

Patient population

Recurrent or metastatic cervical cancer (N=~220)

Part 1: Dose escalation

- 2L+ Arm A: TV (ED) q3w + bevacizumab (ED)
- 2L+ Arm B: TV (ED) q3w + pembrolizumab (FD)
- 2L+ Arm C: TV (ED) q3w + carboplatin (FD)

Part 2: Dose expansion

- 1L Arm D: TV 2 mg/kg q3w + carboplatin
- 1L Arm E: TV 2 mg/kg q3w + pembrolizumab
- 2L/3L Arm F: TV 2 mg/kg q3w + pembrolizumab
- 2L/3L Arm G: TV 2 mg/kg days 1, 8, and 15 of a 28-day cycle
- 1L Arm H: TV 2 mg/kg q3w + pembrolizumab + carboplatin ± bevacizumab

Objectives

Primary objectives

- Part 1: Safety and tolerability (DLTs, MTD, RP2D)
- Part 2: Antitumor activity (ORR by RECIST v1.1)

ED=escalating dose; FD=fixed dose.

Key eligibility criteria

- Recurrent or metastatic cervical cancer
- Progressed on or after SOC therapy (arms A, B, and C only)
- No prior systemic therapy (arms D, E, and H only)
- Progressed on or after 1-2 prior systemic therapies (arms F and G only)
- ECOG PS 0-1

ENGOT PI=Vergote; GOG PI=Monk.

NCT03786081; EUCTR: 2017-004758-40.
1. Clinicaltrials.gov. Accessed October 28, 2022. https://clinicaltrials.gov/ct2/show/NCT03786081. 2. Vergote I, et al. ASCO 2022. Abstract TPS 5603.

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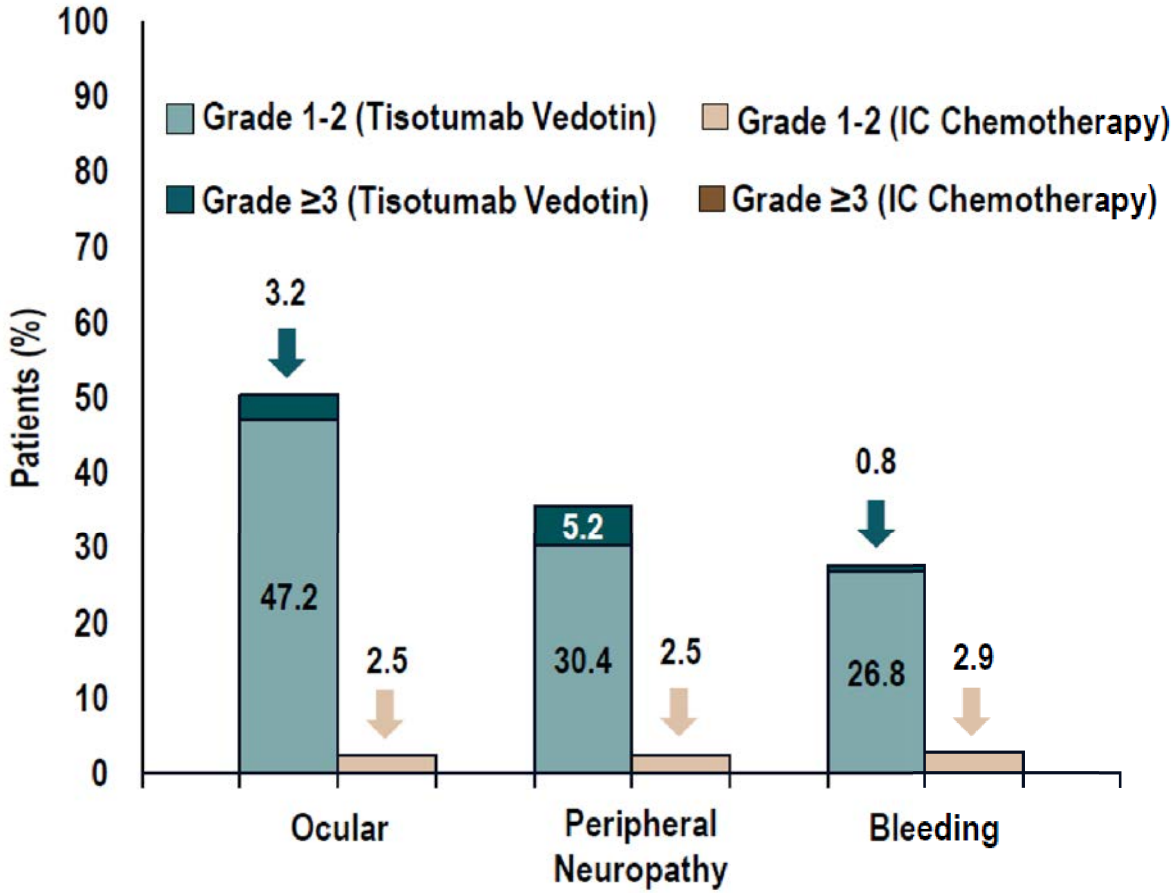
InnovaTV 301: Treatment-Related AEs of Special Interest



- No grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI
Ocular ▪ Conjunctivitis (30.4%) ▪ Keratitis (15.6%) ▪ Dry eye (13.2%)
Peripheral neuropathy ▪ Peripheral sensory neuropathy (26.8% ▪ Paresthesia (2.8%) ▪ Muscular weakness (2.4%) ▪ Peripheral sensorimotor neuropathy (2.4%)
Bleeding ▪ Epistaxis (22.8%) ▪ Hematuria (3.2%) ▪ Vaginal hemorrhage (3.2%)

AESI, adverse event of special interest.

Vergote I, et al. ESMO 2023. Abstract LBA9.

Atrium Health
Levine Cancer Institute

Progress in Cervical Cancer

- Elimination through vaccination and screening
- Decreased morbidity from surgery
- Improved adjuvant therapy
- Addition of Immunotherapy
- Dual Immunotherapy
- Antibody Drug Conjugates - New drug class