EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Updates on Targeted Therapies, ADCs, and Immunotherapy for Advanced or Recurrent Cervical Cancer

Sarah Dilley, MD, MPH, FACOG
Assistant Professor, Division of Gynecologic Oncology

Debates and Didactics in Hematology and Oncology
July 22, 2023

- I have no relevant financial disclosures

Gynecologic Cancers

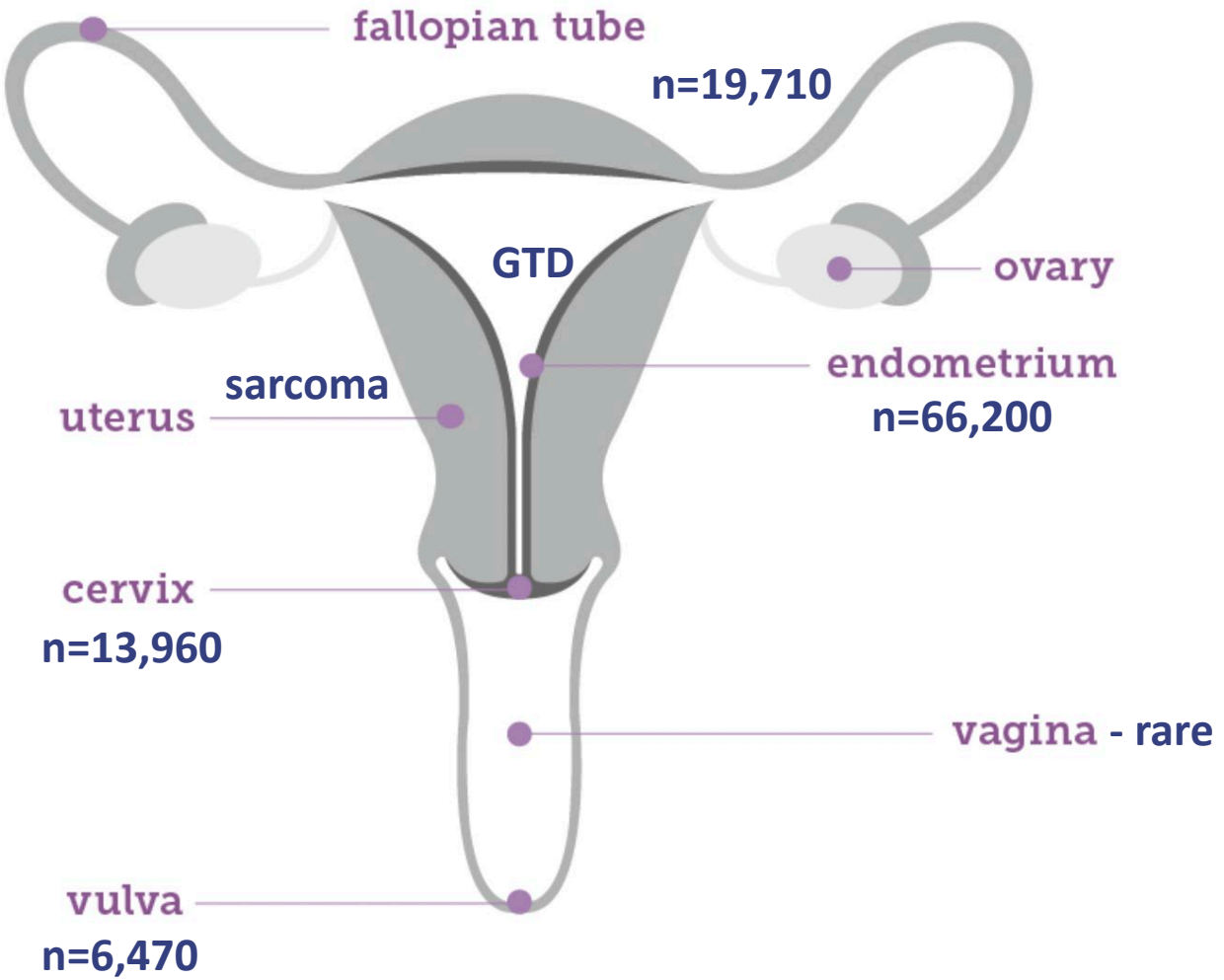


Image: Foundation for Women's Cancer; Data: American Cancer Society. *Cancer Facts & Figures 2023*

Cervical Cancer

- Worldwide – 4th most common cancer in women (WHO)
- Effective screening has decreased incidence and mortality in high-income countries
- Disproportionately affects women of color in both incidence and mortality
  - Incidence rates are higher amongst Black and Hispanic women
- Most women diagnosed between age 35-44
- 90% HPV-mediated

Cervical Cancer

AT A GLANCE

Estimated new cases, 2023	Estimated deaths, 2023	Incidence rates, 2015-2019	Death rates, 2016-2020
13,960	4,310	7.7	2.2
		Average annual rate per 100,000, age adjusted to the 2000 US standard population.	Average annual rate per 100,000, age adjusted to the 2000 US standard population

Cervical

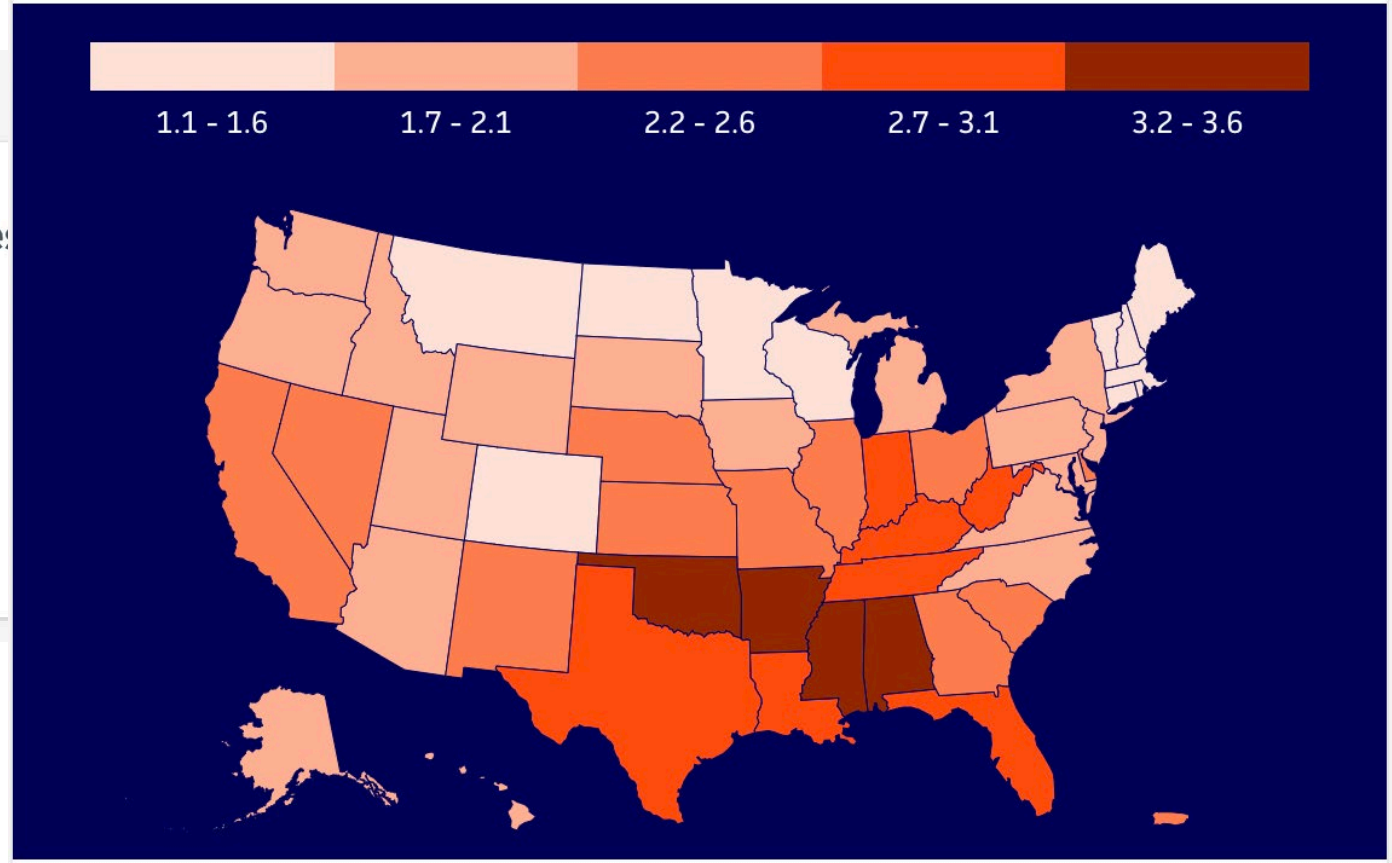
AT A GLANCE

Estimated new cases 2023

13,960

Death rates, 2016-2020

Cervix, by state



Average annual rate per 100,000, age adjusted to the 2000 US standard population

Data sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2022

rates, 2016-2020

2.2

annual rate per 100,000, djusted to the 2000 US tandard population

Cervical Cancer

- Historically underestimated due to lack of accounting for hysterectomy rates
- Huge racial disparities – disparity underestimated by 44%

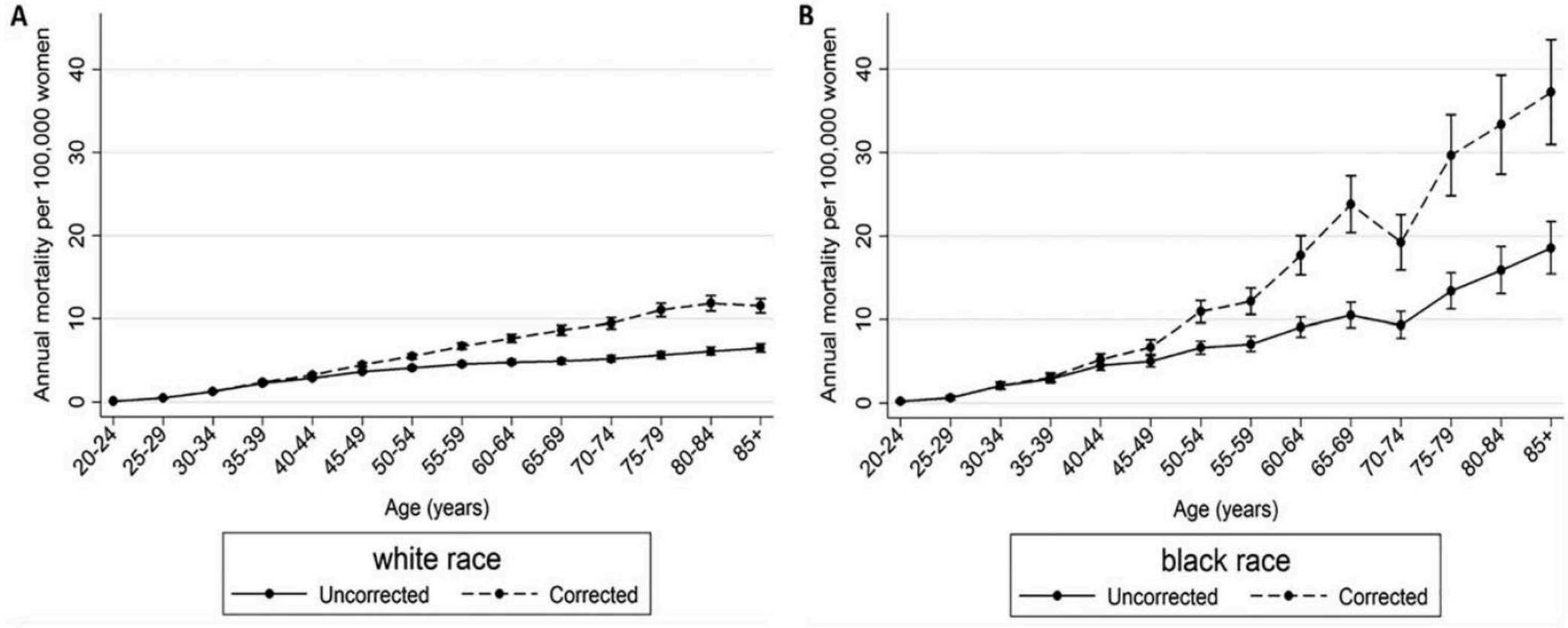
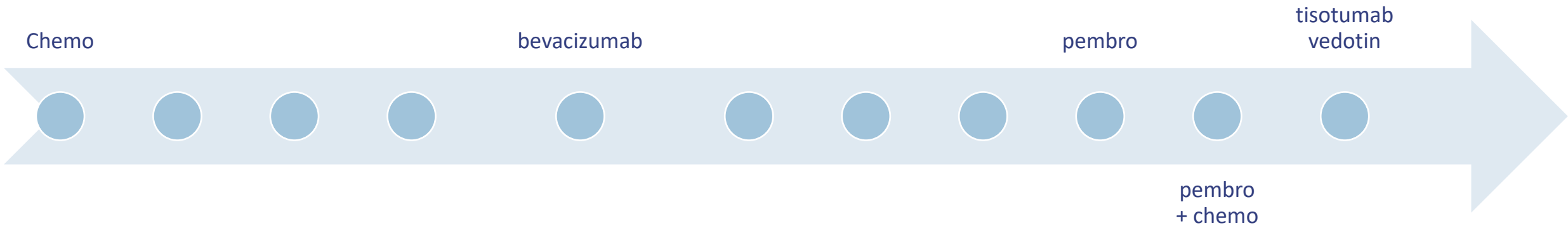


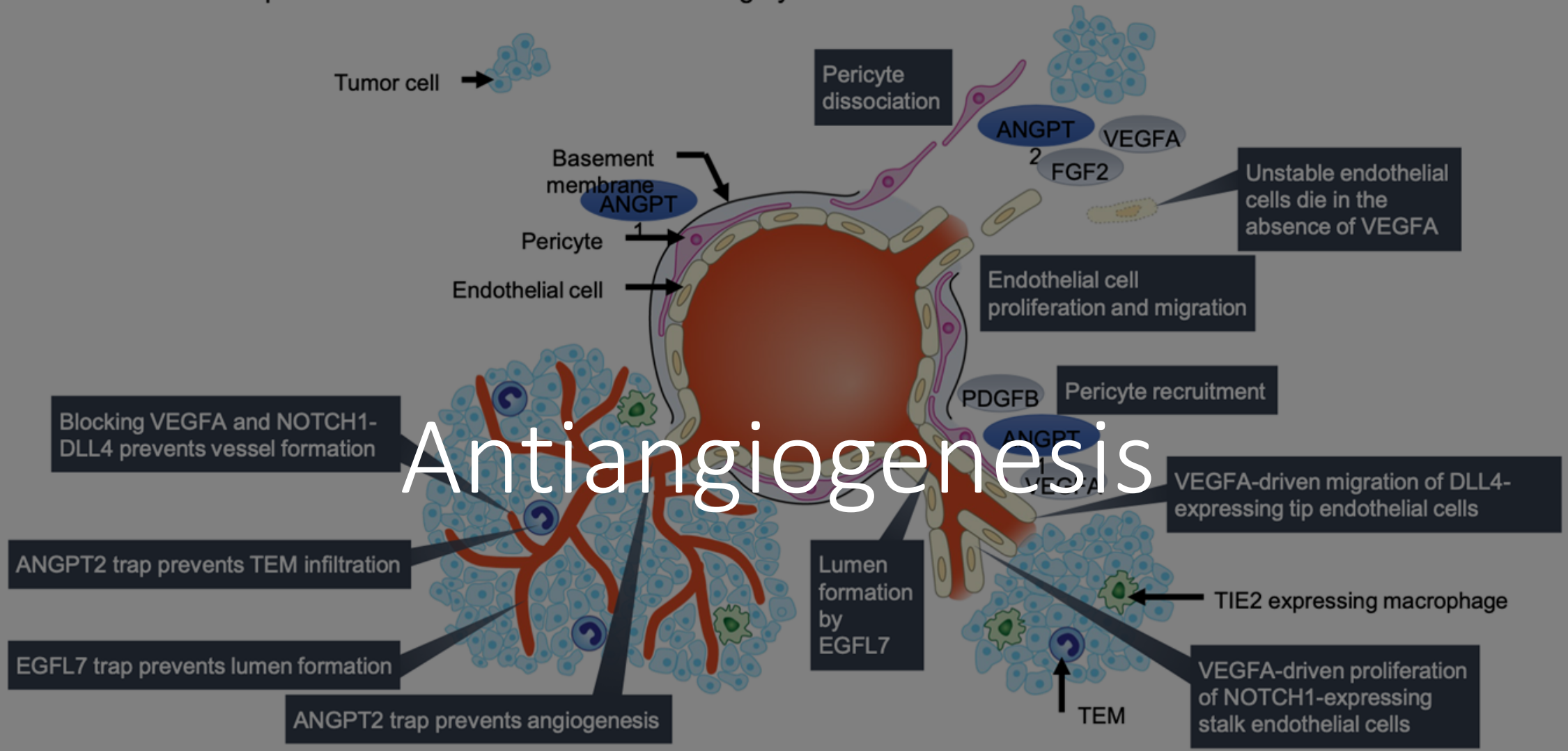
Figure 3. Age-specific cervical cancer mortality rates, uncorrected and corrected for the prevalence of hysterectomy, in (A) white and (B) black women.

Beavis et al. 2017

Cervical Cancer



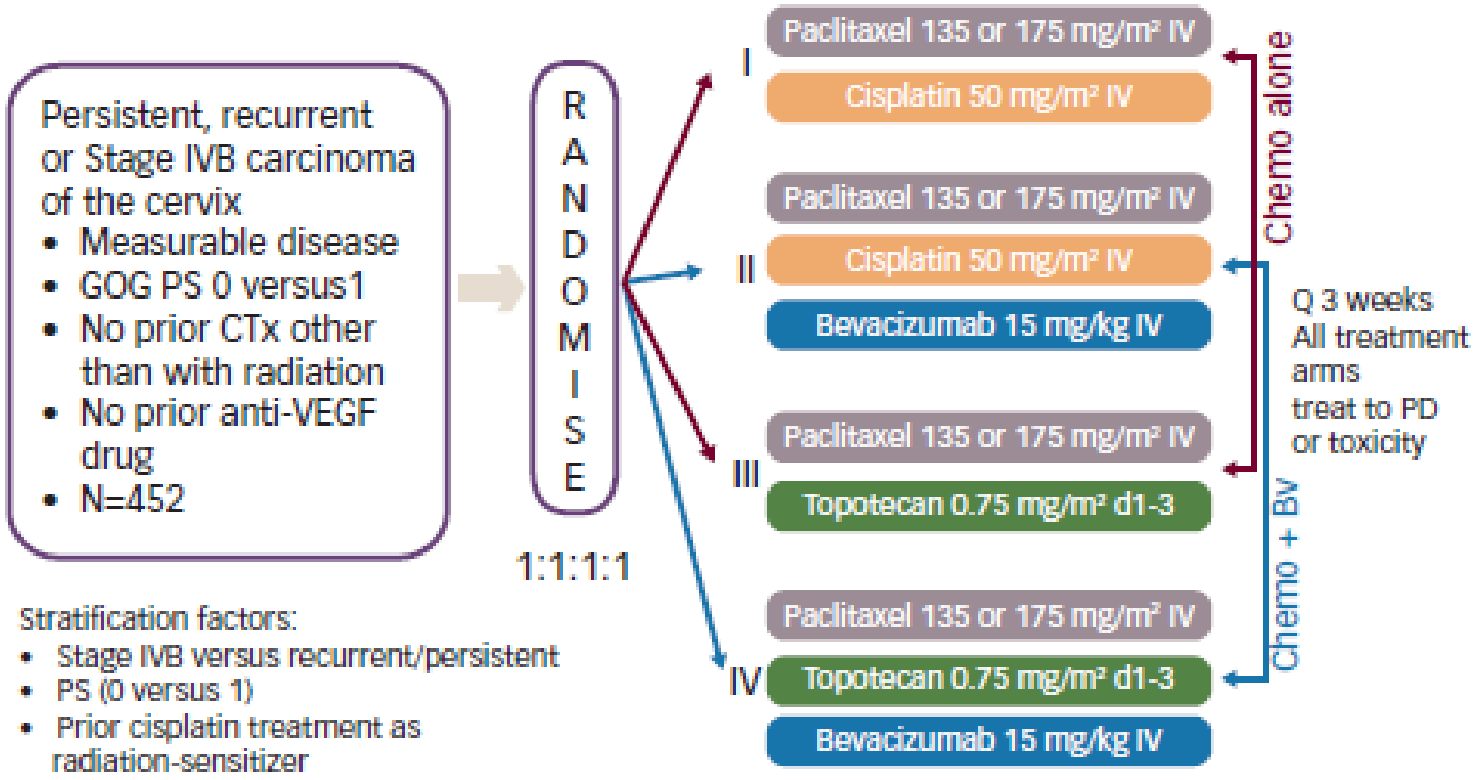
Antiangiogenesis



Adapted from Huang et al, *Nat Rev Cancer* 2010;10:575-585.

Antiangiogenesis – GOG 240

Figure 3: GOG-240 study design



Bv = bevacizumab; CTx = chemotherapy; IV = intravenous; GOG = Gynecologic Oncology Group; PS = performance status; VEGF = vascular endothelial growth factor.

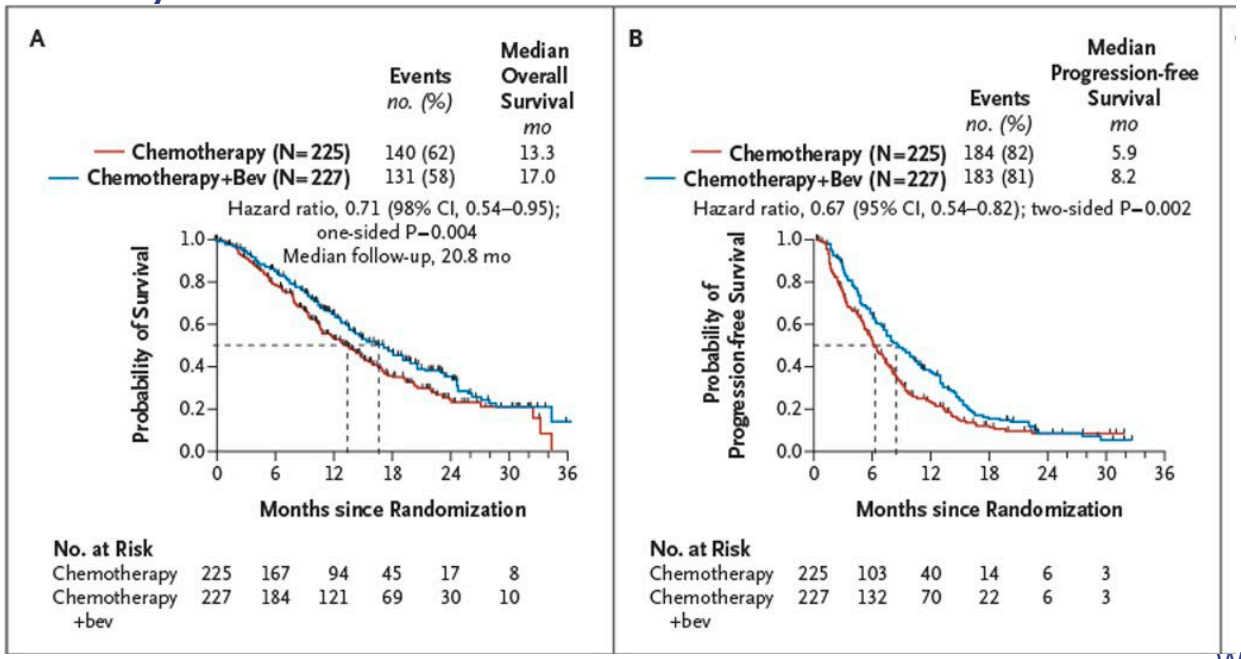
Tewari et al. 2014

Bevacizumab in addition to chemotherapy in advanced cervical cancer

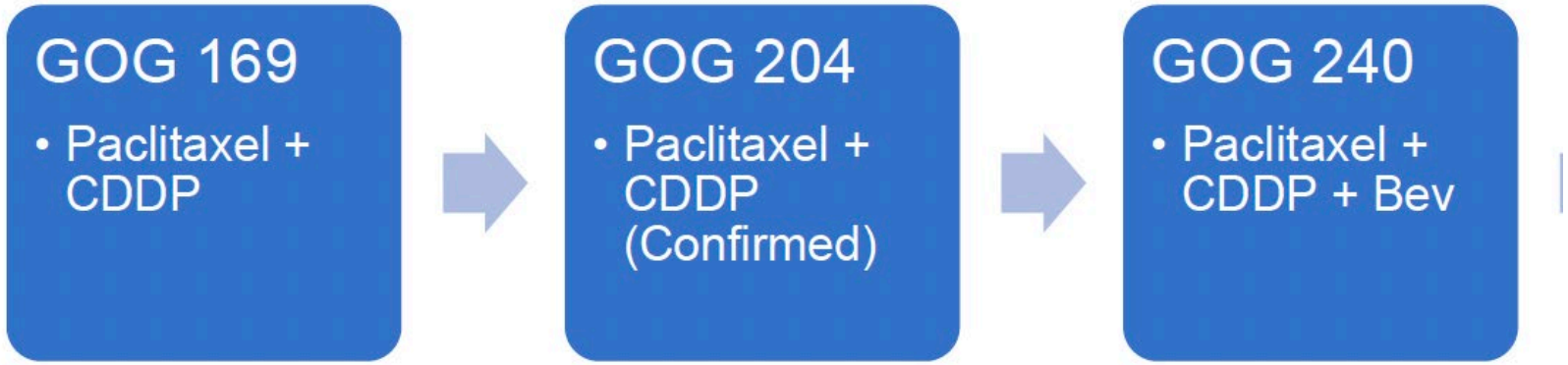
2x2 factorial design

Antiangiogenesis – GOG 240

- **Addition of bevacizumab increased median OS by 4 months without affecting the quality of life: 13.3 vs 17.0 median OS**
- Specific vasculature-related toxicities
  - hypertension, gastrointestinal perforations, venous thromboembolic events, delayed wound healing, **fistula formation**, nephrotic syndrome
  - Patient selection is key…



Antiangiogenesis – GOG 240

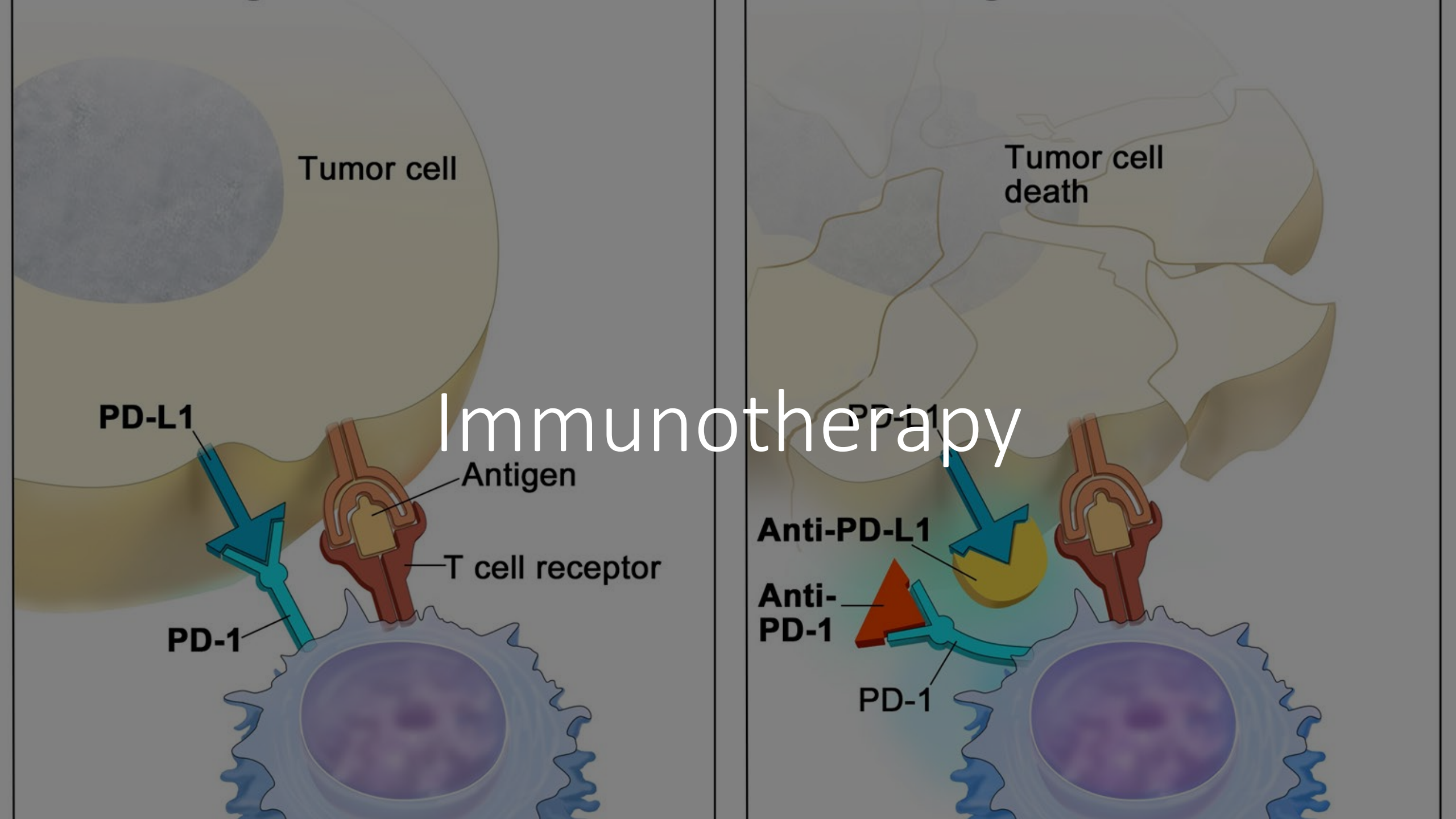


RR 36%
PFS 4.8 mo
OS 9.7 mo

RR 29.1%
PFS 5.8 mo
OS 12.9 mo

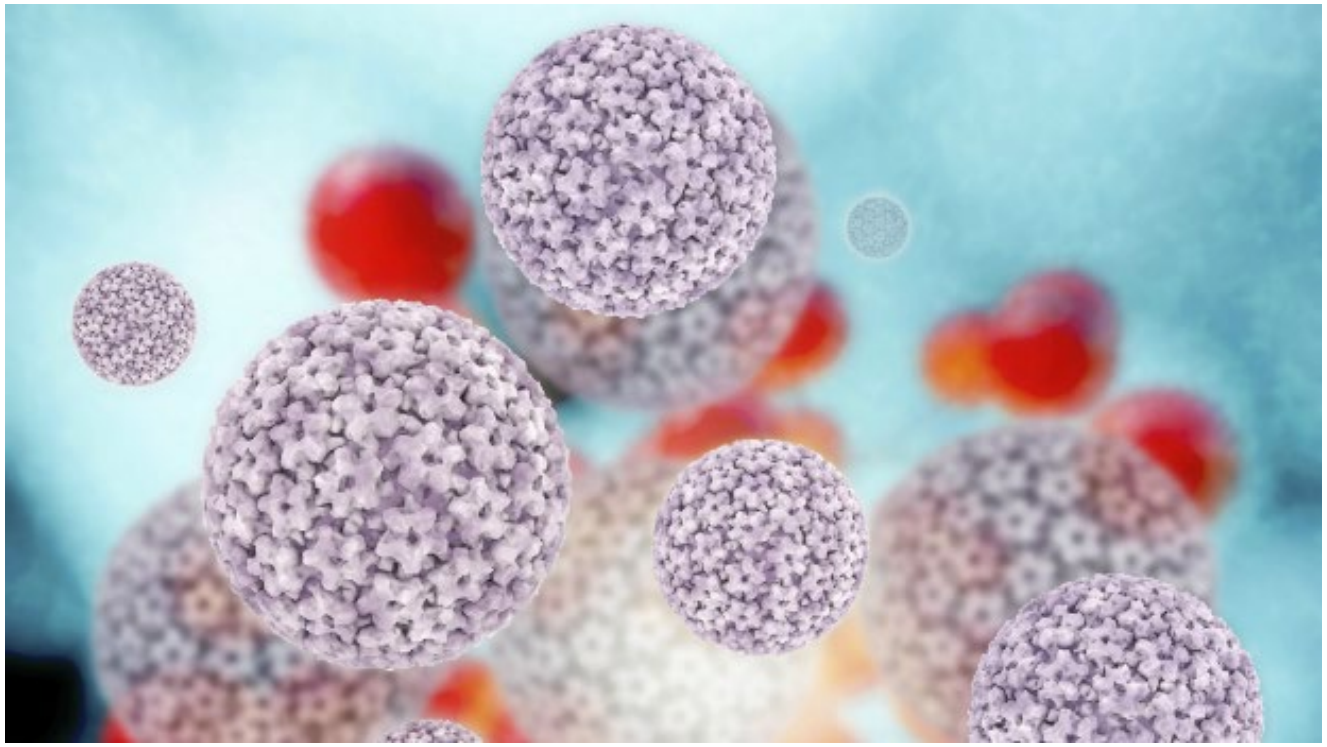
RR 50%
PFS 8.2 mo
OS 16.8 mo

Immunotherapy



Immunotherapy

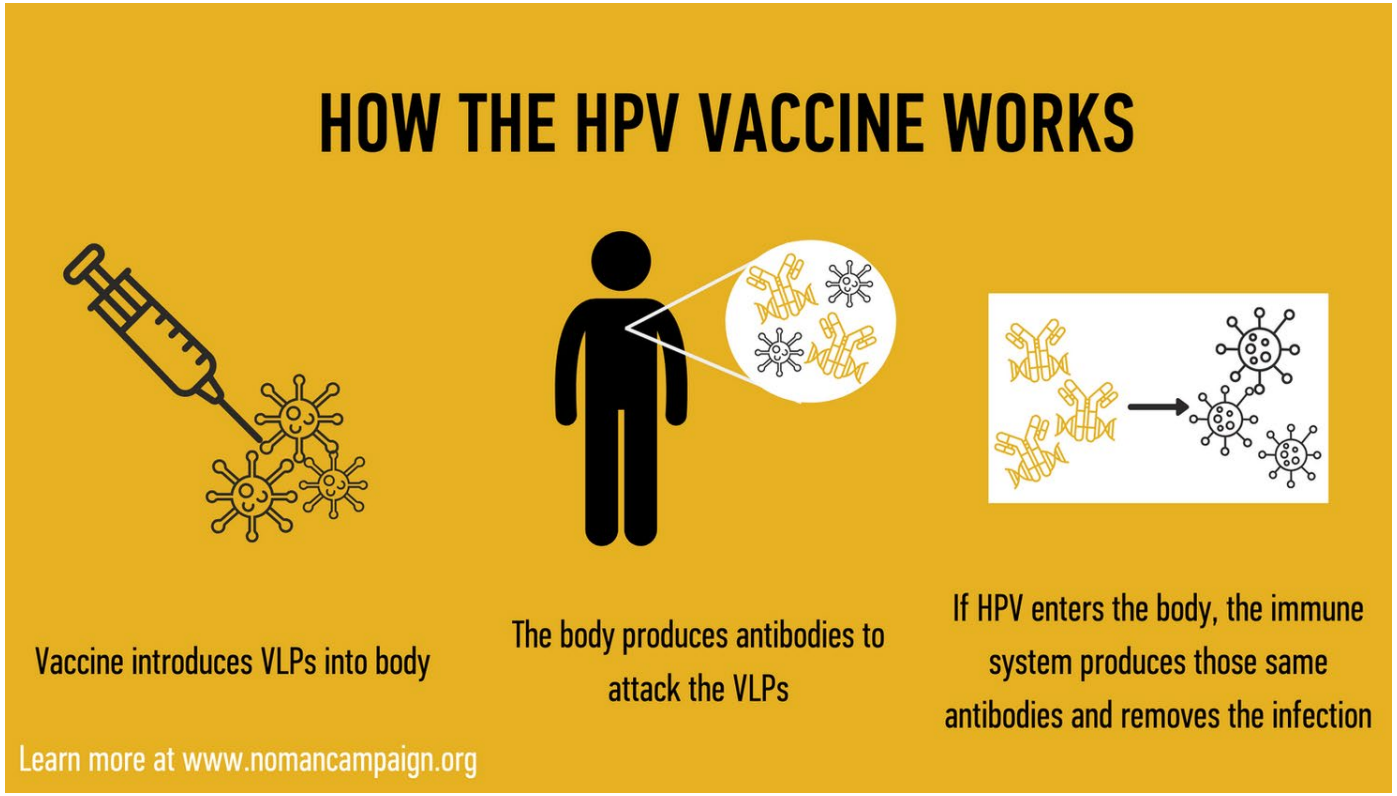
- Prevention
- Treatment



Immunotherapy

- **Vaccines = the ultimate immune therapy!**

- Only the nonovalent currently available in the US
- Recombinant L1 capsid protein virus-like particle (VLP)
- 9 strains: 6,11,**16,18**,31,33,45,52,58

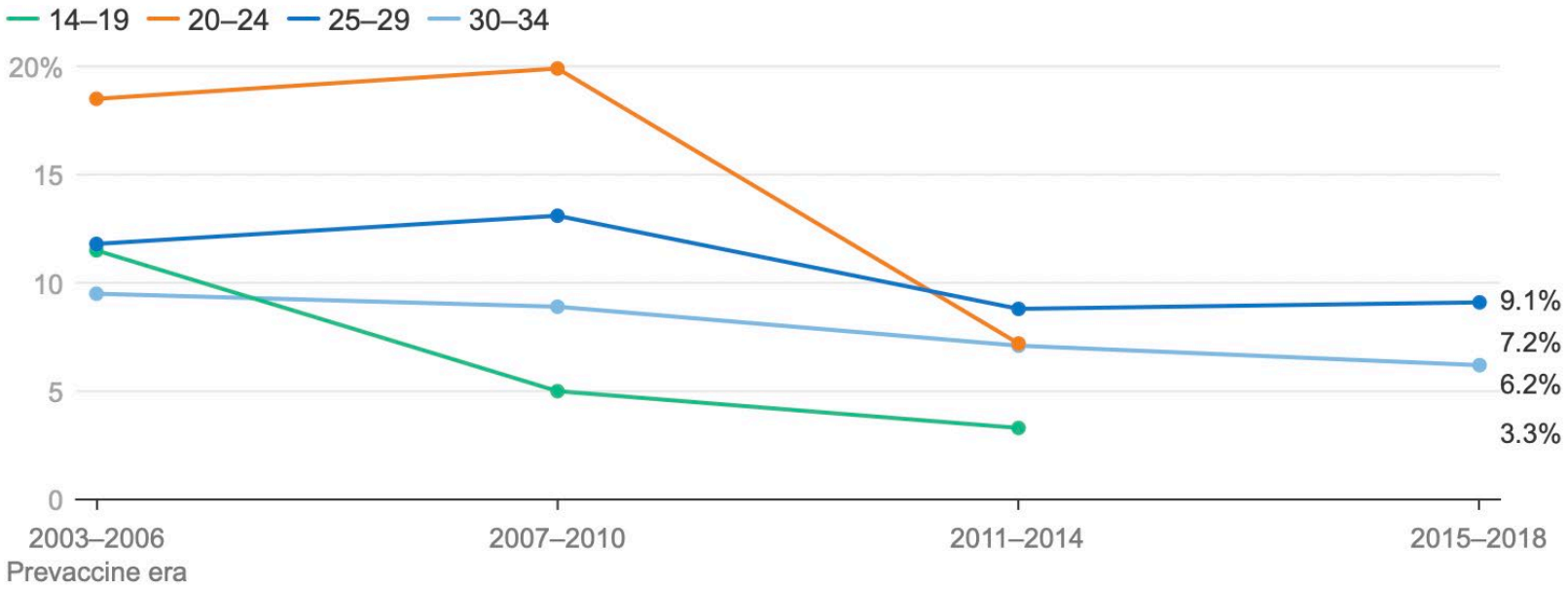


Immunotherapy – HPV vaccine

Figure 3

Prevalence of HPV Infections Have Drastically Declined Among Teenage Girls and Young Women Since the Introduction of the Vaccine

Prevalence of 4vHPV-type infections among women 14-34



NOTE: 4vHPV = HPV 6, 11, 16, or 18. 2015-2018 data for ages 14-19 and 20-25 not included, relative standard error >30% and ≤50%, considered unstable.

SOURCE: Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of Vaccine — United States, 2003–2018. MMWR Morb Mortal Wkly Rep 2021;70:415–420 • PNG

KFF

Immunotherapy – HPV vaccine

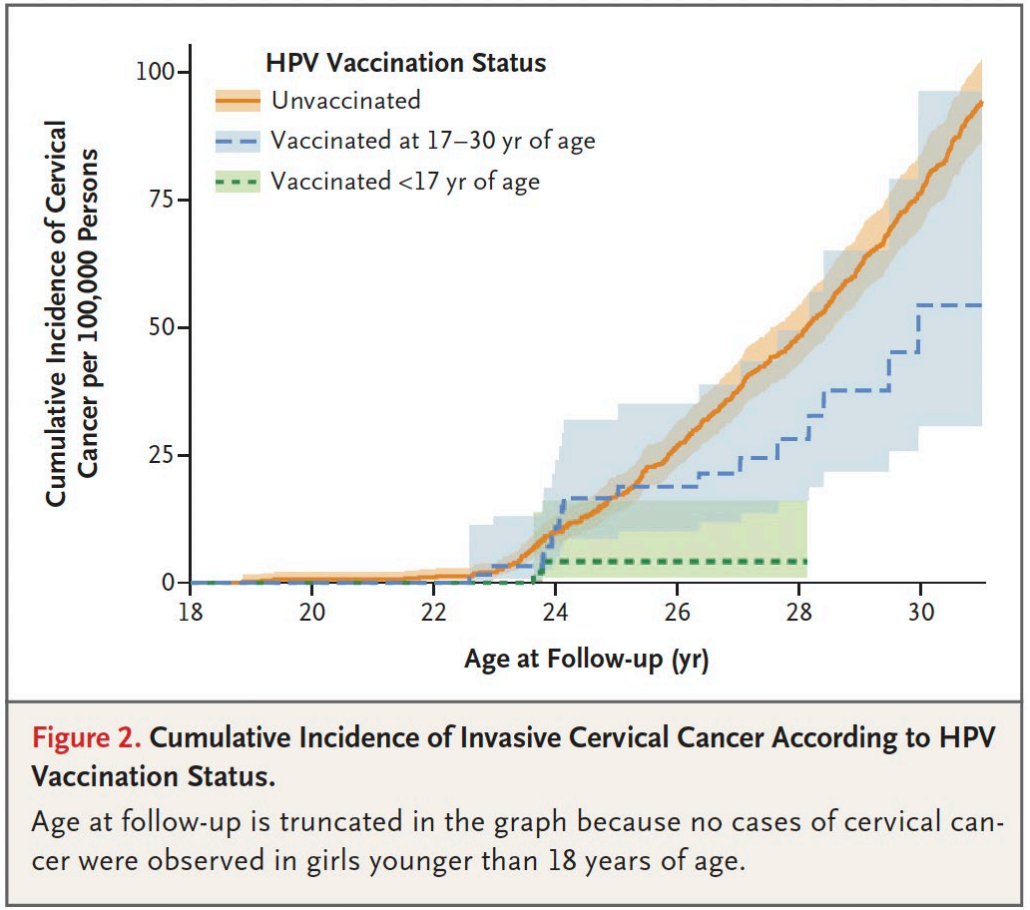


Figure 2. Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.

Age at follow-up is truncated in the graph because no cases of cervical cancer were observed in girls younger than 18 years of age.

- Lei et al. 2020
- 1.5 million Swedish females age 10-30
- 2006-2017
- Cancer in 19 vaccinated women (4vHPV) and 538 unvaccinated
- Adjusted IRR for vaccinated <17yo: **0.12** (95% CI, 0.00 to 0.34)

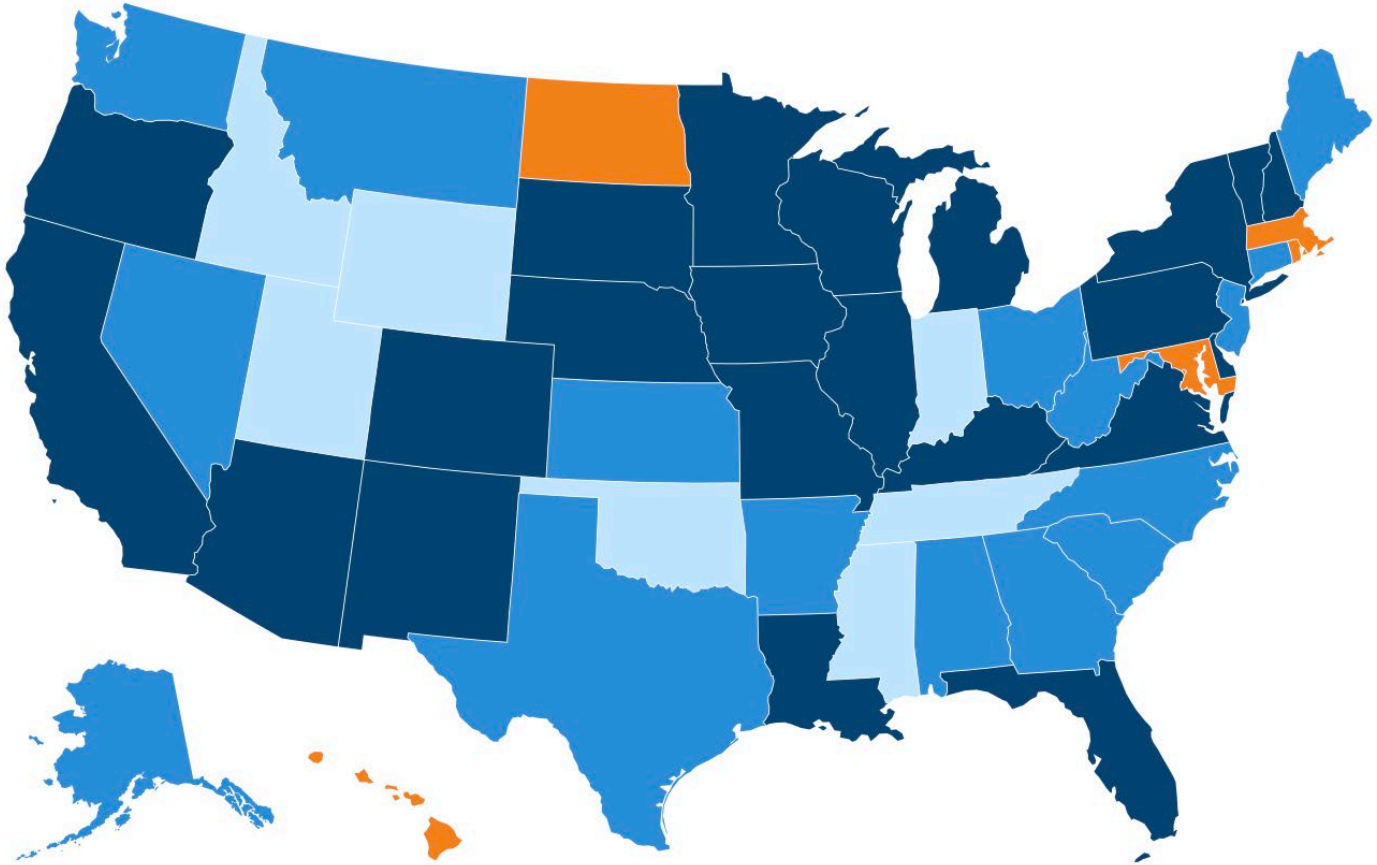
Lei J et al. N Engl J Med 2020;383(14):1340-1348.

HPV Vaccination Rates of Adolescents, by State

Adolescents ages 13-17 with HPV Up-to-Date (UTD) Vaccination Series, 2019

Estimated vaccine coverage for adolescents ages 13-17

< 46.7% | 46.7%–54.3% | 54.3%–64.0% | ≥ 64.0%



NOTE: HPV UTD includes those with ≥ 3 doses, and those with 2 doses when the first HPV vaccine dose was initiated prior to age 15 years and there was at least 5 months minus 4 days between the first and second dose. In DC, 75.5% of adolescents are HPV UTD. DC requires female students to start HPV vaccine series prior to entering 6th grade.

SOURCE: CDC. SUPPLEMENTARY TABLE. Estimated vaccination coverage with selected vaccines and doses* among adolescents aged 13–17 years† (N = 18,788) by HHS region, state, selected local area, or territory — National Immunization Survey–Teen (NIS-Teen), United States, 2019. August 2020; National Conference of State Legislatures. HPV Vaccine: State Legislations and Regulation. Accessed April 2021.

• PNG

KFF

HPV Vaccine Schedule and Dosing

Routine vaccination	Age **11–12 years**; can be started at age 9 years
Catch-up Vaccination*	Age **13–26 years**, if not adequately vaccinated
Shared clinical decision-making*	Some adults age **27–45 years**, if not adequately vaccinated

*MMWR. 2019;68(32);698-702

HPV Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices: www.cdc.gov/hpv/hcp/schedules-recommendations.html

HPV Vaccine

- For cervical cancer precursors - CIN2/3
- Virus-like particle (VLP) vaccines:
  - Adjuvant treatment
- DNA Vaccines: VGX-3100*
  - Alternative to excision?

*not FDA-approved

HPV Vaccine

Proposed mechanism of action:

- Cross protection against other strains
- Change in immune microenvironment after excision
- Prevention of re-infection or auto-inoculation

Systematic Review

Adjuvant Human Papillomavirus Vaccine to Reduce Recurrent Cervical Dysplasia in Unvaccinated Women

A Systematic Review and Meta-analysis

Katie Lichter, MPH, Danielle Krause, MD, Jingwen Xu, MD, MPH, Sung Huang Laurent Tsai, MD, MPH, Camille Hage, MD, MPH, Erica Weston, MD, Ahizechukwu Eke, MD, MPH, and Kimberly Levinson, MD, MPH

HPV Vaccine

- Meta-analysis
- n=2984, 6 studies
- Examined recurrence risk of CIN2+ after excisional procedure +/- adjuvant HPV vaccine
- Risk reduction of recurrence:
  - CIN1 33%
  - **CIN2+ 64%**
- 1.9% vs 5.9% recurrence rate

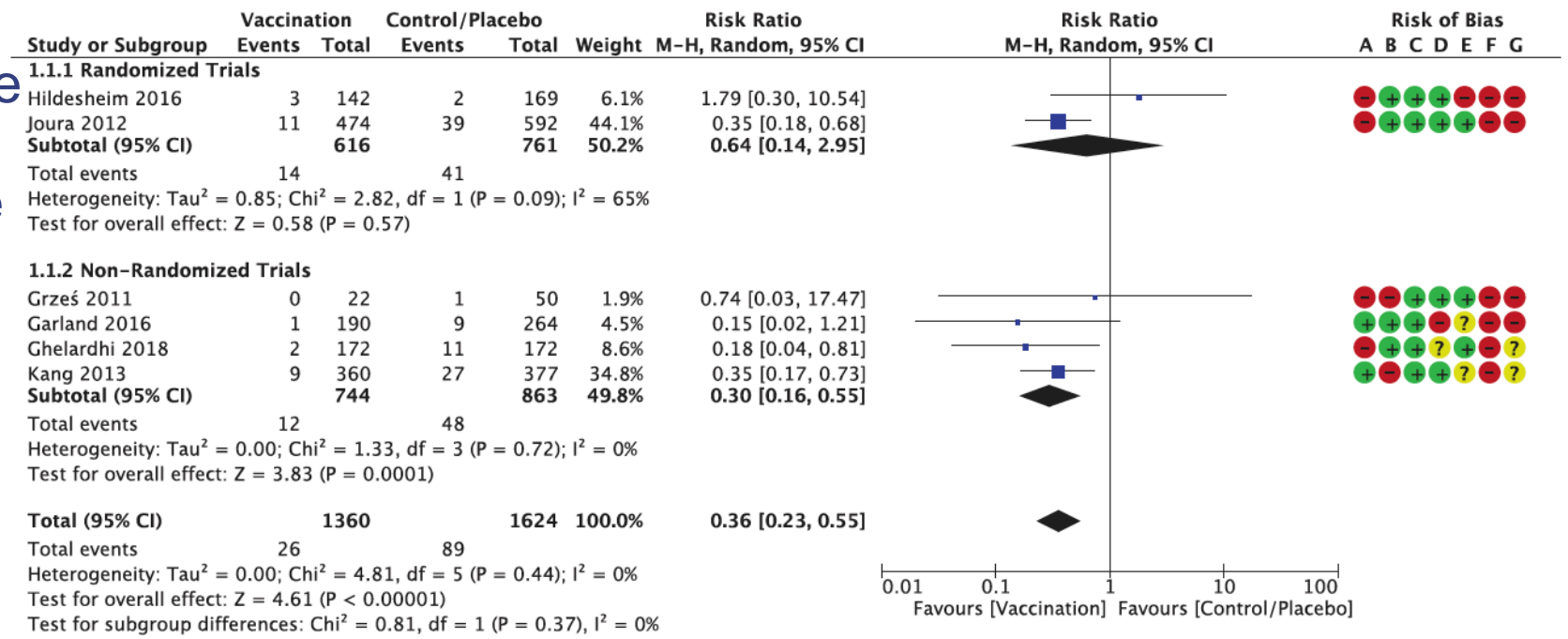
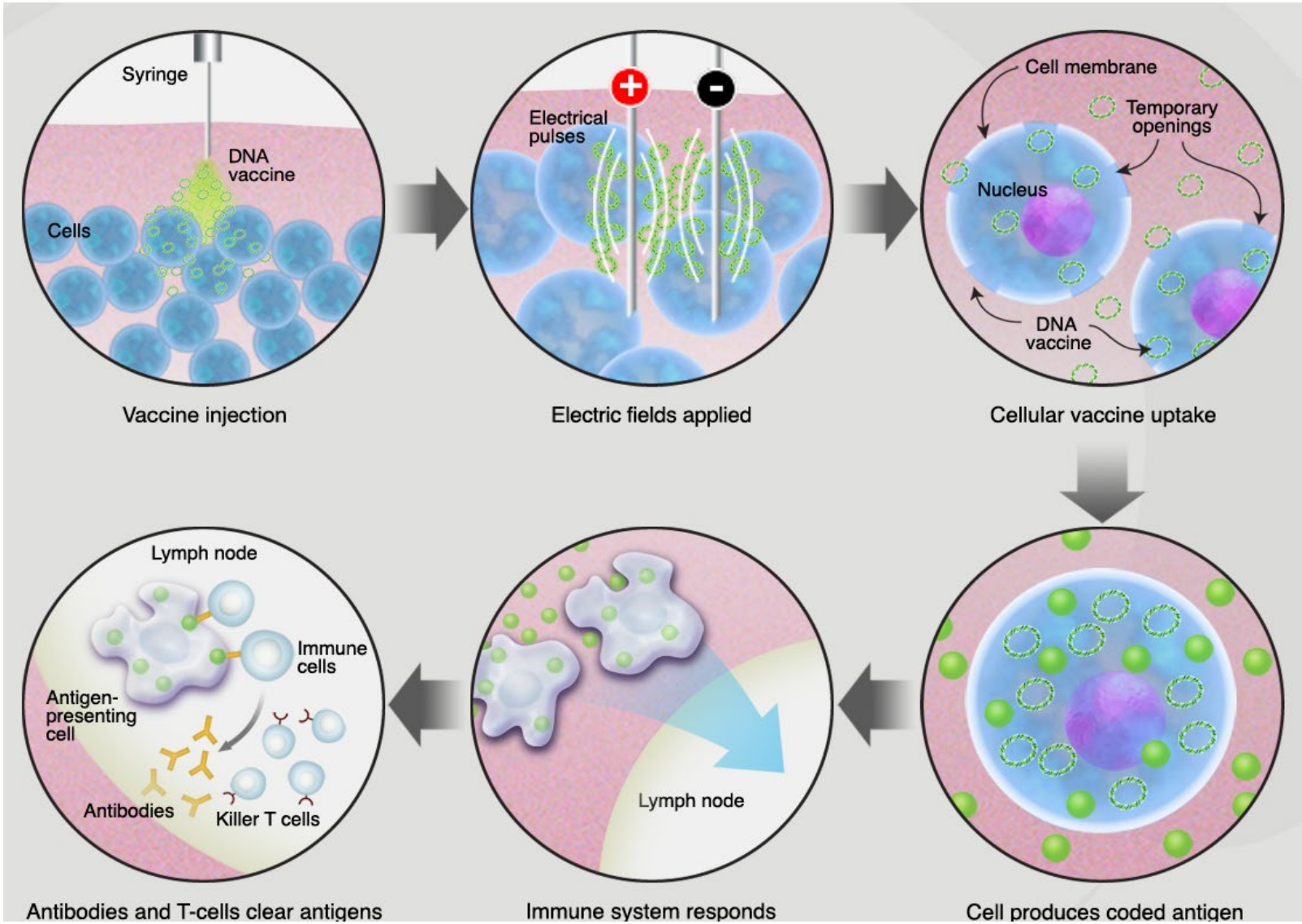


Fig. 4. Forest plot of the risk of cervical intraepithelial neoplasia 2 or greater recurrence with comparison of human papillomavirus (HPV) vaccination vs control (irrespective of HPV type). I^2 statistic represents the interstudy heterogeneity as

Immunotherapy – HPV DNA Vaccines

- VGX 3100: DNA vaccine
- Targets HPV 16/18 E6/E7 proteins
- IM injection
- Better delivery required to make DNA vaccines work→to induce T cell response and drive T cells to the tumor
- *In vivo* electroporation



VGX-3100 CIN2/3 Phase 2 Study Design

Placebo-Controlled, Randomized, Double Blind

- 148 subjects: 18-55 year old females with high-grade cervical dysplasia (CIN2/3)
- HPV 16 and/or 18 positive
- 6 mg VGX-3100 or placebo(IM followed by EP) at weeks 0, 4, and 12

Primary Endpoint

- Regression of CIN2/3 to CIN1 or normal at six months post third dose (Week 36)

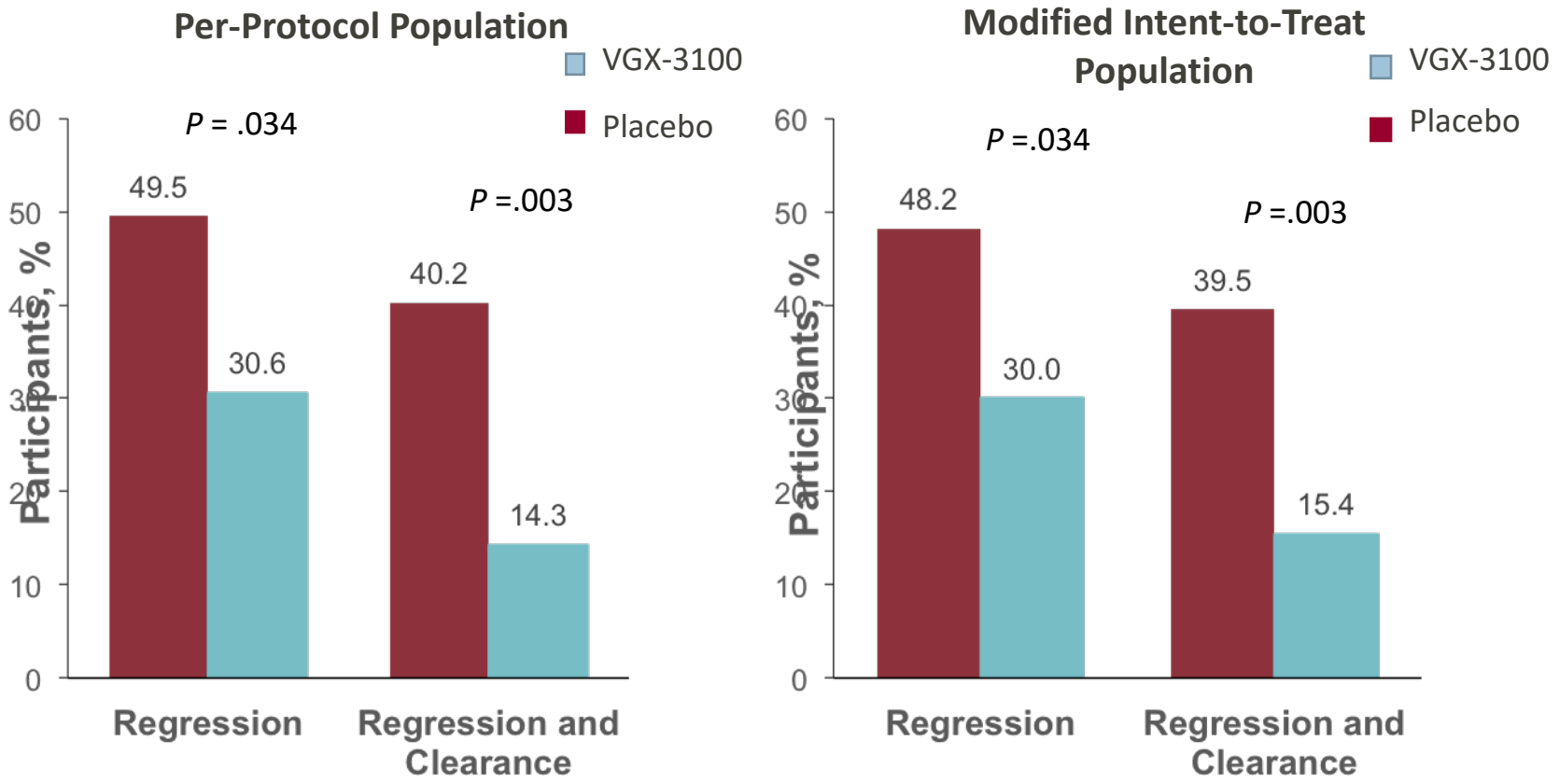
Secondary Endpoint

- Regression of CIN2/3 to CIN1 or normal and
- Clearance of HPV 16 and/or 18 genotype detected during screen

Trimble CL, et al. *Lancet.* 2015;386:2078–2088

Immunotherapy – HPV DNA Vaccines

Phase II Trial: 48.2% vs 39.5% regression to CIN1 or clearance in the ITT population



Trimble CL, et al. *Lancet.* 2015;386:2078–2088; slides courtesy of Dr. Warner Huh

VGX-3100

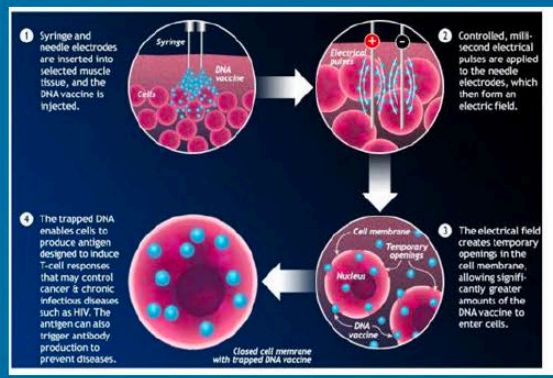
- PHASE III trial REVEAL 1
  - 193 patients with confirmed HPV16/18 CIN2/3
  - Prospective RCT of VGX-3100 Delivered by Electroporation With CELLECTRA™-5PSP
  - Endpoints – histologic regression and HPV clearance
  - 23.7% vs. 11.3% clearance (p=0.02)

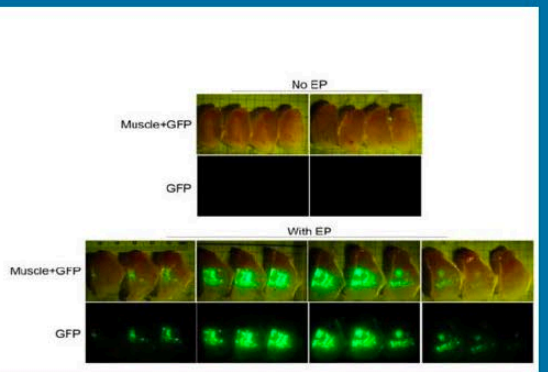
INOVIO
POWERING DNA MEDICINES™

NEWS RELEASE

INOVIO Announces Positive Results from REVEAL 1, a Phase 3 Pivotal Trial Evaluating VGX-3100, its DNA-based HPV Immunotherapy for the Treatment of High-grade Precancerous Cervical Dysplasia Caused by HPV-16 and/or HPV-18

3/1/2021





Sardesai, Current opin Immunol, 2011

Slide courtesy of Dr. Kim Levinson

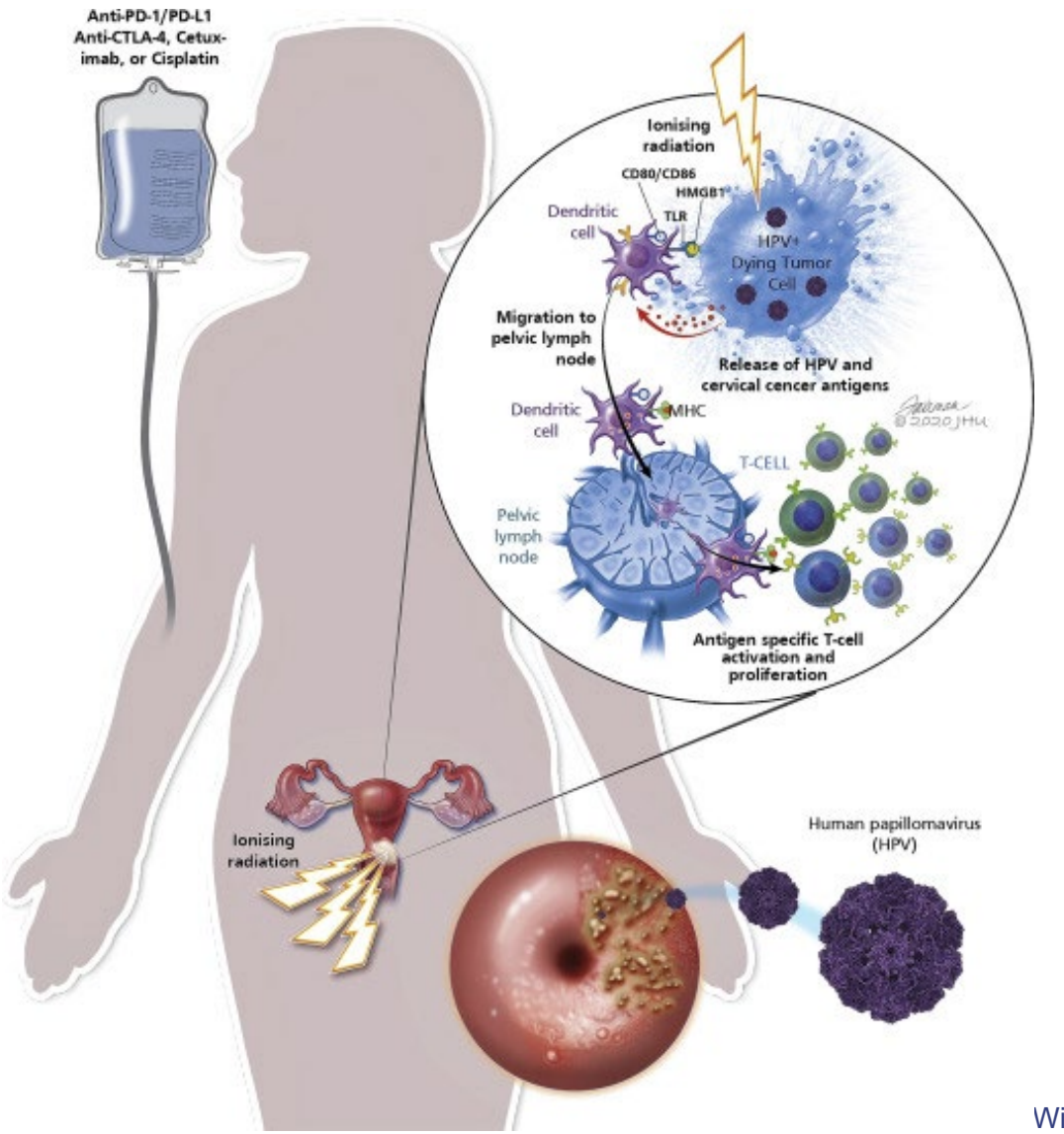
Immunotherapy – HPV DNA Vaccines

- What about actual cancer?

- **GOG 3091**
- "*A Single Arm, Open Label, Multicenter Phase 2 trial to Evaluate the Efficacy and Safety of VB10.16 used in Combination with CPI (TBD) in Patients with HPV16 Positive, Recurrent or Metastatic Cervical Cancer who are Refractory to Combination Chemotherapy and Pembrolizumab and/or Bevacizumab*"
  - A Randomized, Double-Blind, Placebo-Controlled Phase 2 trial:
    - Compare study drug with placebo to study drug with checkpoint inhibitor
    - Intramuscular injections of a DNA-based immunotherapy
    - Intravenous infusions of placebo or checkpoint inhibitor

Immunotherapy – Checkpoint inhibitors

- Multiple mechanisms by which HPV alters the immune response
- Neoantigen production by viral infection
- T cell activation

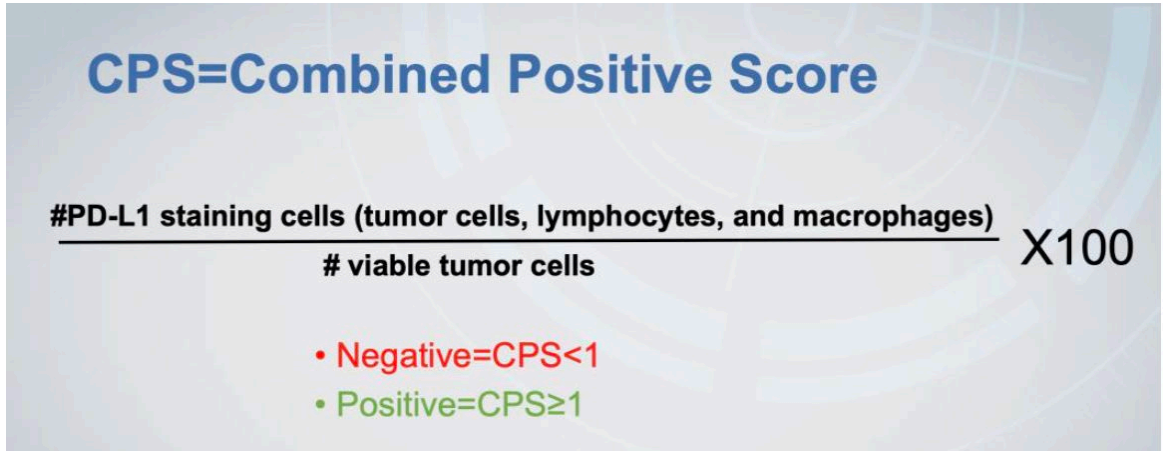


Immunotherapy – Checkpoint inhibitors

- KEYNOTE- 028: first study showing checkpoint inhibition with pembrolizumab has activity
  - Progressed on prior chemotherapy, PDL1>1%
  - 17% ORR

- KEYNOTE-158: 98 patients with advanced cervical cancer, irrespective of PDL-1 expression → 13% response rate

- Checkpoint-358: nivolumab
  - 26% response rate with CPS >/=1



Immunotherapy – Checkpoint inhibitors

- KEYNOTE-158: 98 patients with advanced cervical cancer
  - PD-L1 pos 14.3% ORR
  - PD-L1 neg – no responses

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

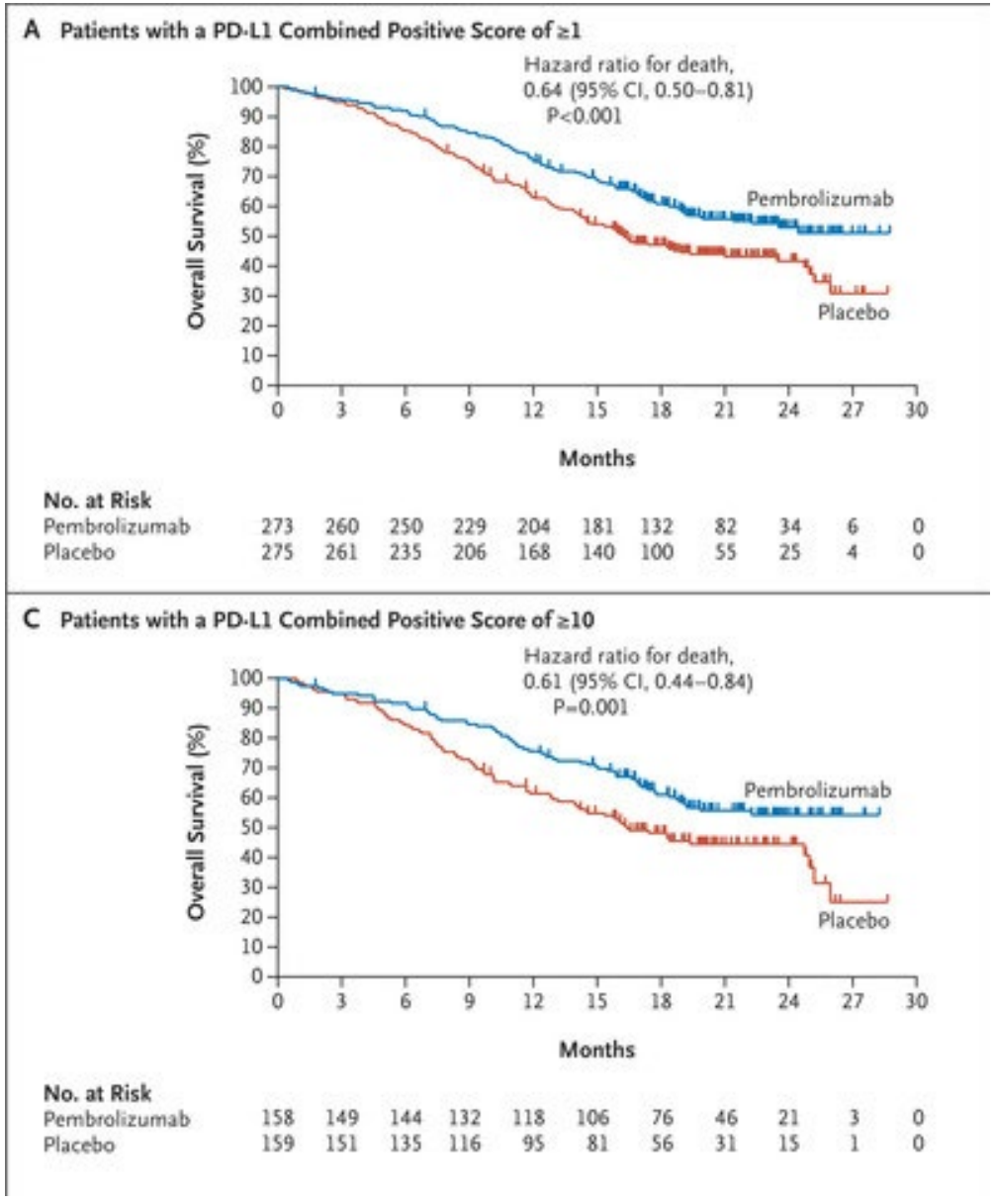
Share Tweet Linkedin Email Print

On June 12, 2018, the Food and Drug Administration approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Immunotherapy – Keynote 826

- KEYNOTE- 826: Upfront chemotherapy- no prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy were permitted)
  - Platinum-based chemo
    - +/- bevacizumab – investigator's discretion
    - +/- pembrolizumab q21 days – randomized 1:1
  - Pembrolizumab was continued for 24 months or until disease progression/unacceptable toxicity
  - 617 patients randomized

Immunotherapy – Keynote 826



- CPS >/= 1
  - Median PFS 10.4 vs 8.2
  - OS at 24 months: 50.4 vs 40.4% (HR 0.65, CI 0.5-0.81)
- CPS >/= 10
  - Median PFS 10.4 vs 8.1
  - **OS at 24 months: 54.4% vs 44.6% (HR 0.61, CI 0.44-0.84)**

Colombo et al. 2021, NEJM

Immunotherapy – Keynote 826

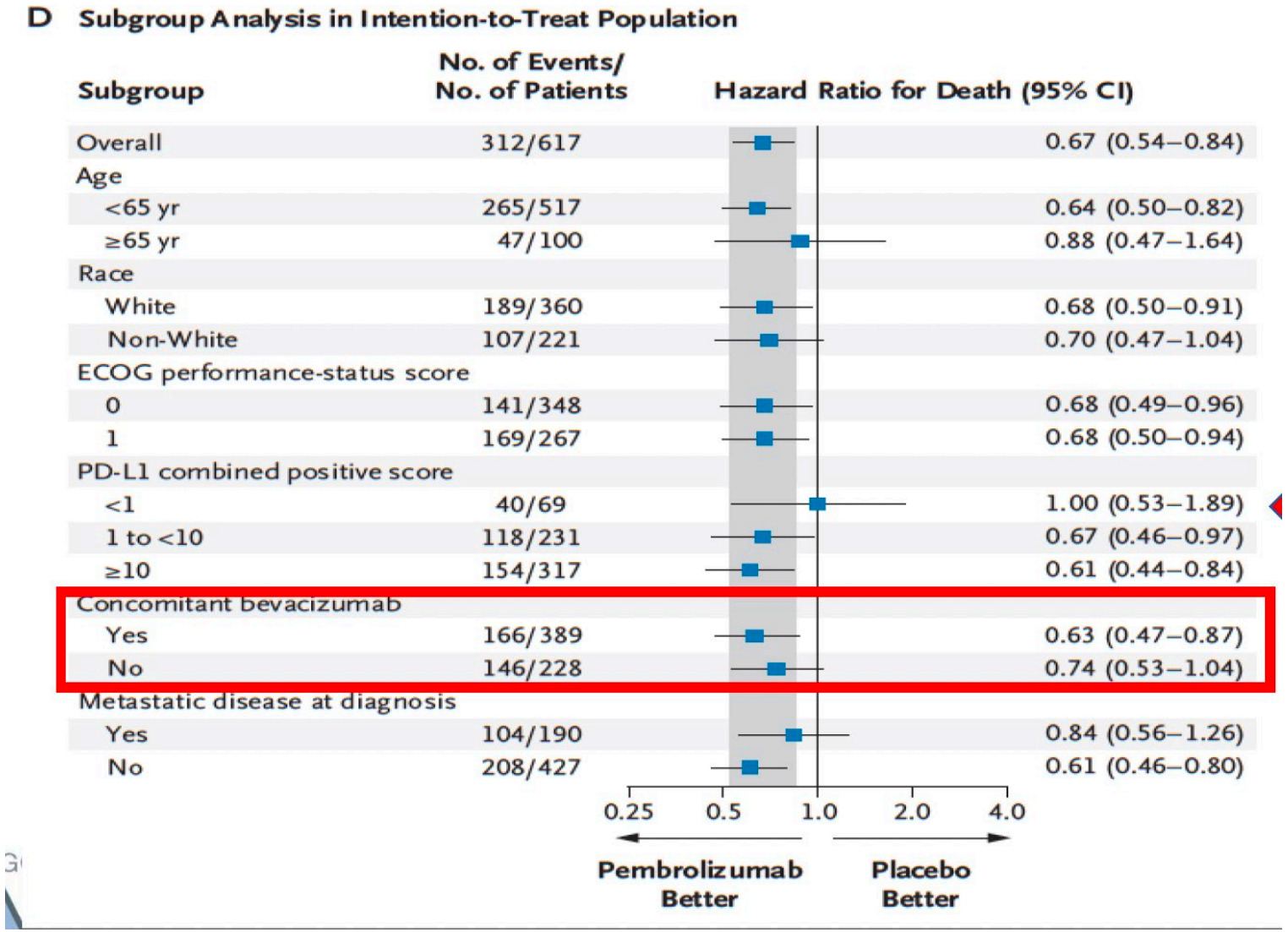
FDA approves pembrolizumab combination for the first-line treatment of cervical cancer

Share | Tweet | Linkedin | Email | Print

On October 13,2021, the Food and Drug Administration approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS≥1), as determined by an FDA-approved test.

Colombo et al. 2021, NEJM

Immunotherapy – Keynote 826



Colombo et al. 2021, NEJM

Immunotherapy – Keynote 826

Updated 3 year survival data

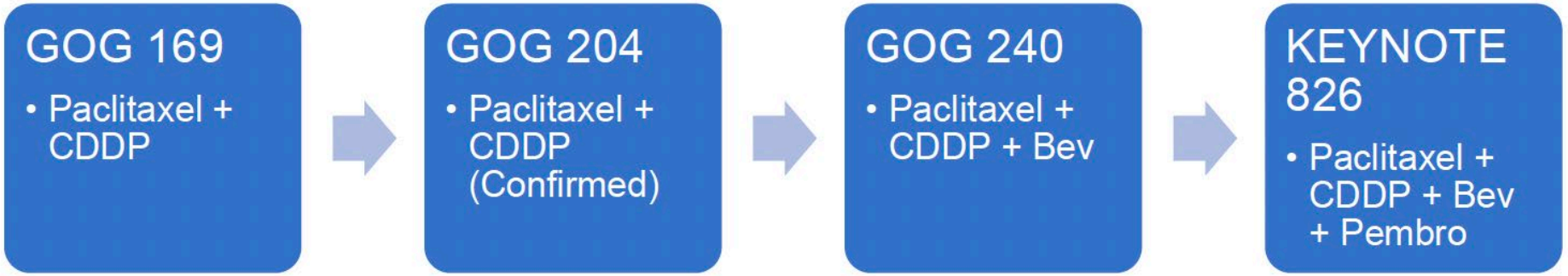
ORR: PD-L1+ (48% of patients) =29%, Overall population: 19%

Benefit seen regardless of bev use

	PD-L1 CPS ≥1		All-Comer		PD-L1 CPS ≥10	
	Pembro + Chemo n = 273	Pbo + Chemo n = 275	Pembro + Chemo n = 308	Pbo + Chemo n = 309	Pembro + Chemo n = 158	Pbo + Chemo n = 159
OS, median, mo	28.6	16.5	26.4	16.8	29.6	17.4
24-mo OS rate, %	53.5	39.4	52.1	38.7	54.4	42.5
OS, HR (95% CI)	0.60 (0.49-0.74); *P*< 0.0001		0.63 (0.52-0.77); *P*< 0.0001		0.58 (0.44-0.78); *P*< 0.0001	
PFS, median, mo	10.5	8.2	10.4	8.2	10.4	8.1
12-mo PFS rate, %	45.6	33.7	44.7	33.1	44.7	33.5
PFS, HR (95% CI)	0.58 (0.47-0.71); *P*< 0.0001		0.61 (0.50-0.74); *P*< 0.0001		0.52 (0.40-0.68); *P*< 0.0001	

Abstract presented at ASCO 2023, Monk et al

Immunotherapy



RR 36%
PFS 4.8 mo
OS 9.7 mo

RR 29.1%
PFS 5.8 mo
OS 12.9 mo

RR 50%
PFS 8.2 mo
OS 16.8 mo

RR 68.1%
PFS 10.4 mo
OS 53% at 2 yrs
OS ITT 24.4 mo

Courtesy of Dr. Trey Leath

Immunotherapy – Keynote A18

Phase 3 KEYNOTE-A18 Trial Met Primary Endpoint of Progression-Free Survival (PFS) in Patients With Newly Diagnosed High-Risk Locally Advanced Cervical Cancer

Save

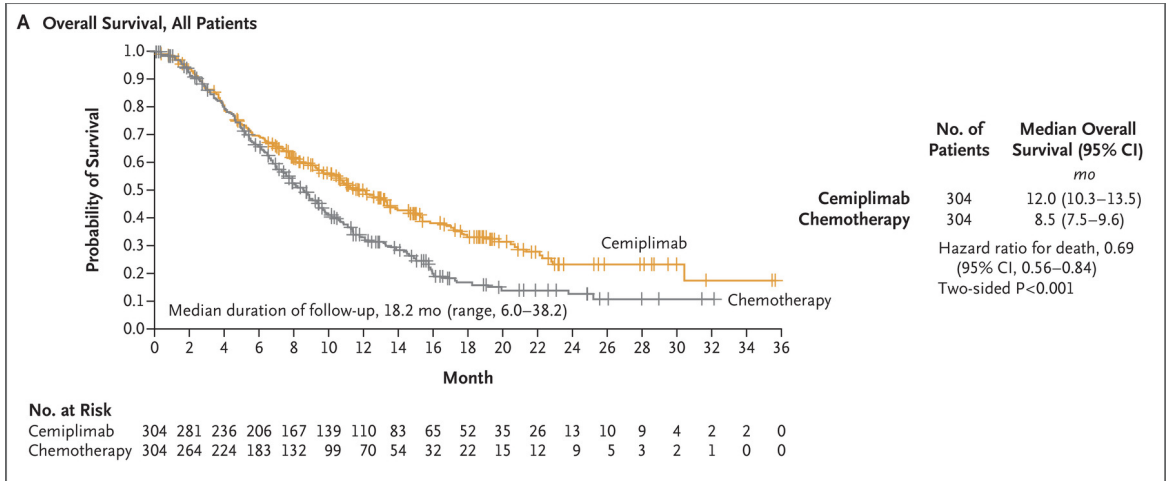
July 19, 2023 6:45 am ET

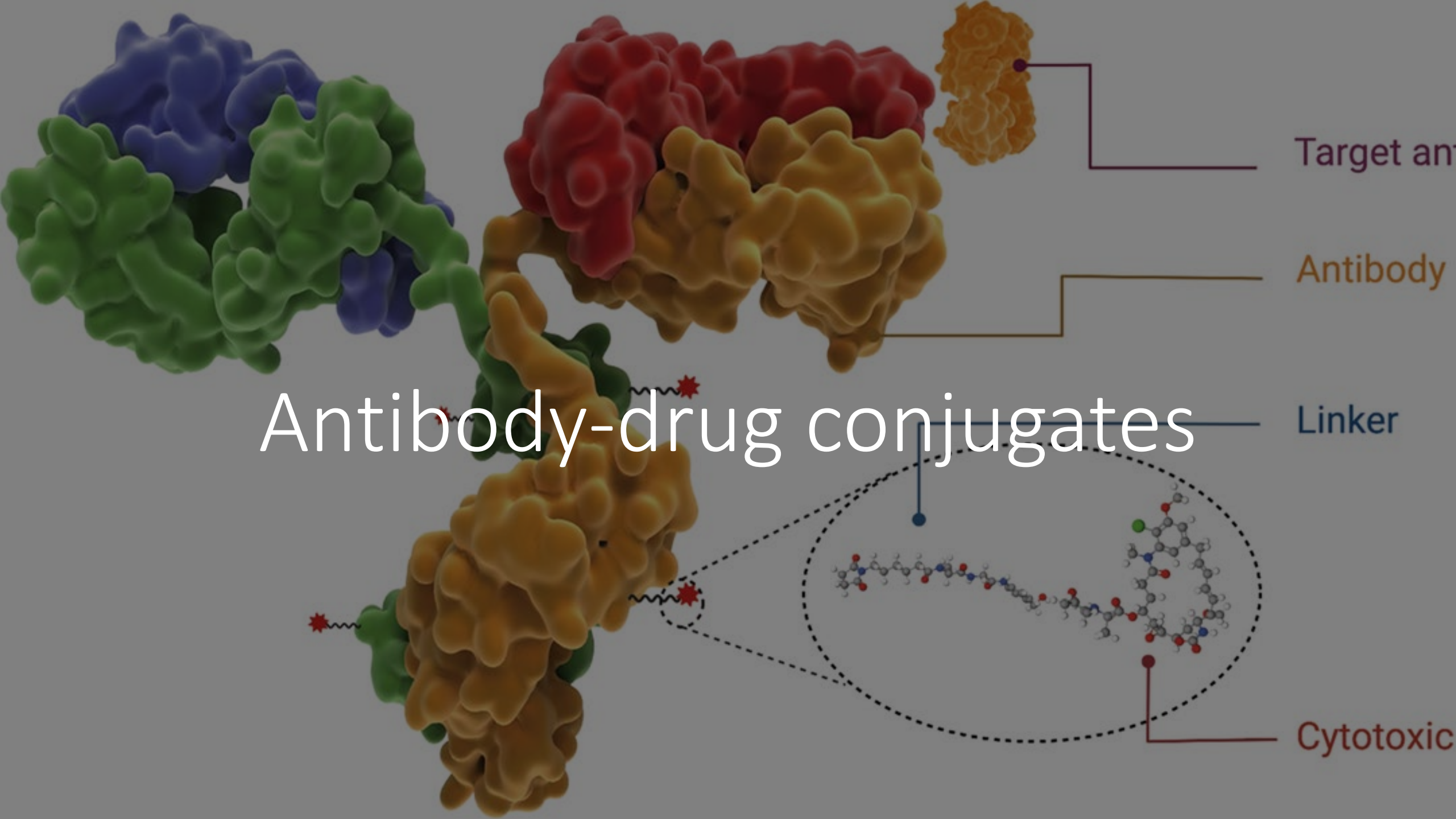
(pembrolizumab) plus concurrent chemoradiotherapy demonstrated statistically significant and clinically meaningful improvement in PFS versus concurrent chemoradiotherapy alone in these patients

Immunotherapy – cemiplimab

Cemiplimab vs. single-agent chemo in recurrent cervical cancer

- PD-1–blocking mAb approved to treat lung and skin cancers
- Phase 3 trial, 608 women enrolled
- 1 Prior platinum-based chemotherapy, regardless of PD-L1 status
- Results:
  - **OS longer in the cemiplimab group vs. chemo group (12.0mo vs. 8.5 mo; HR, 0.69; 95% CI 0.56- 0.84; two-sided P<0.001)**
  - **RR 16% vs. 6.3%**

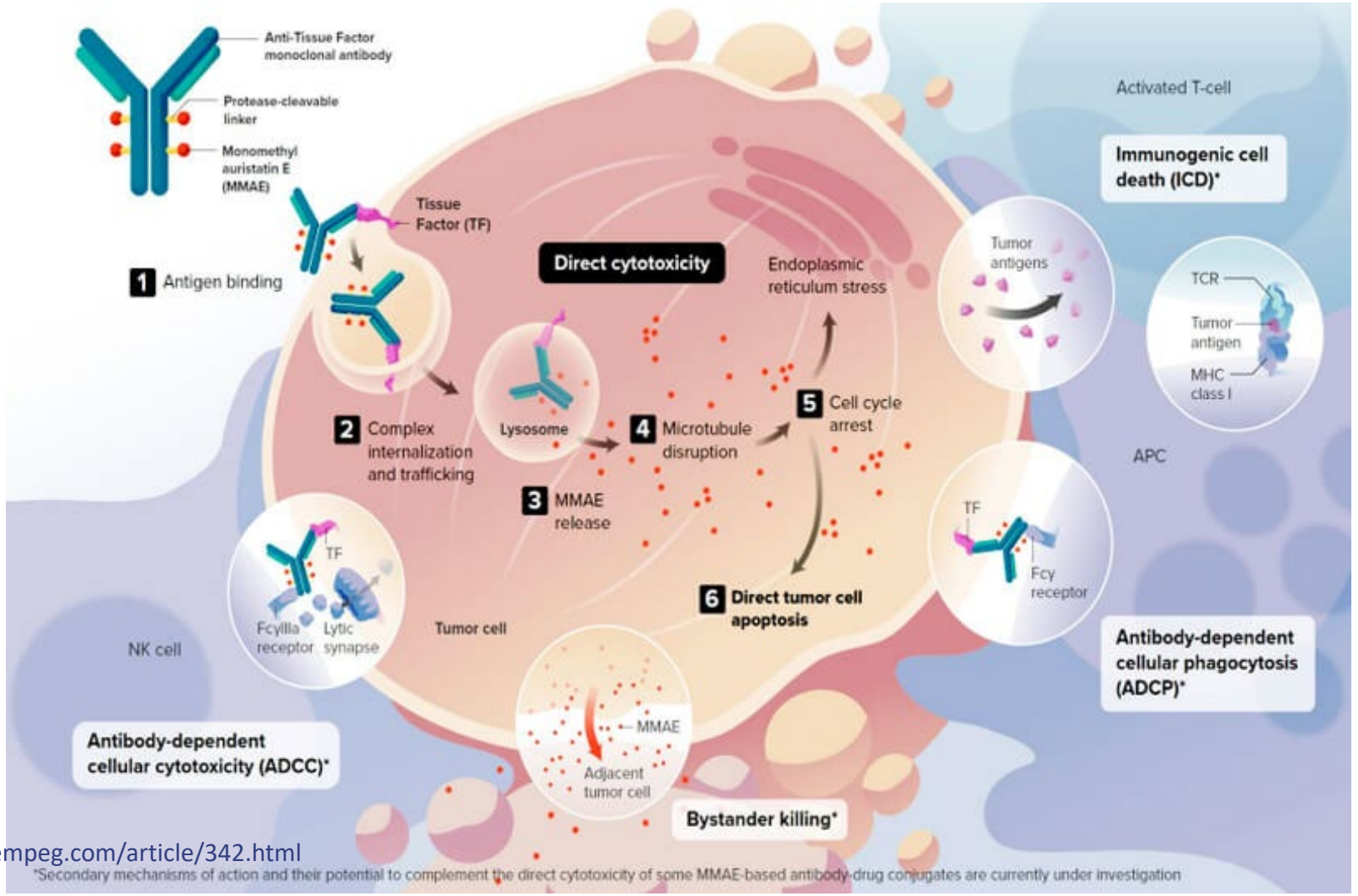




Antibody-drug conjugates

ADCs – Tisotumab Vedotin

- A tissue factor-directed ADC linked to a potent microtubule inhibitor

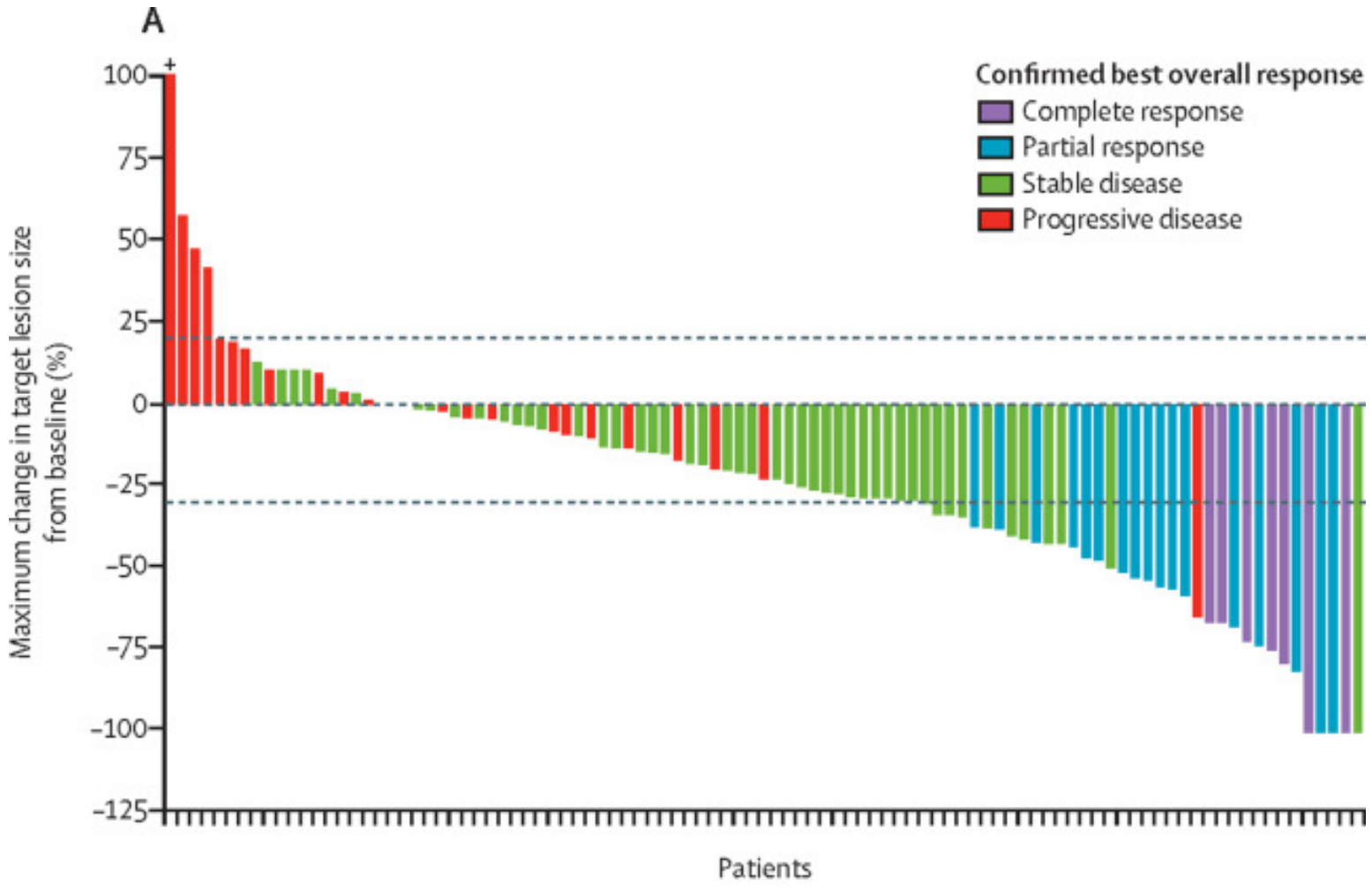


www.biochempeg.com/article/342.html

ADCs – Tisotumab Vedotin

- InnovaTV 204 (NCT03438396; Coleman et al., 2021) phase 2 study, 101 patients with recurrent metastatic disease who failed platinum-based chemotherapy +/- bev
- ORR was **24%** (95% CI: 16%, 33%) and the duration of response was 8.3 months
  - Compares favorably to historical 2nd-line treatment (~15)
  - 7% CR, 17% PR
- Toxicity:
  - Taxol- like side effects- neuropathy, fatigue
  - **Ocular – dryness, erythema, irritation, blurry vision, vision loss**
  - FDA approval September 2021

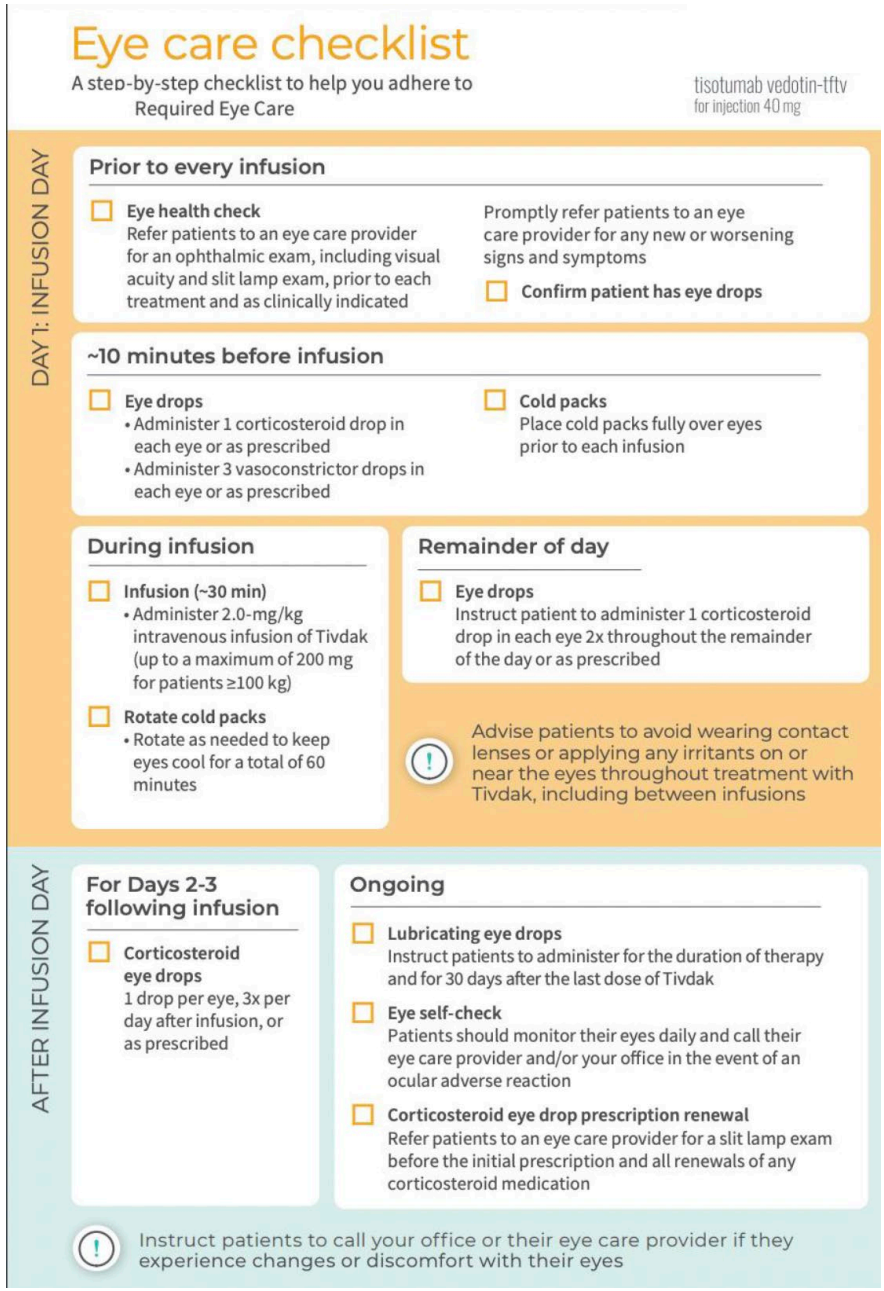
ADCs – Tisotumab Vedotin



ADCs – Tisotumab Vedotin

- **Challenging in the cervical cancer patient population**

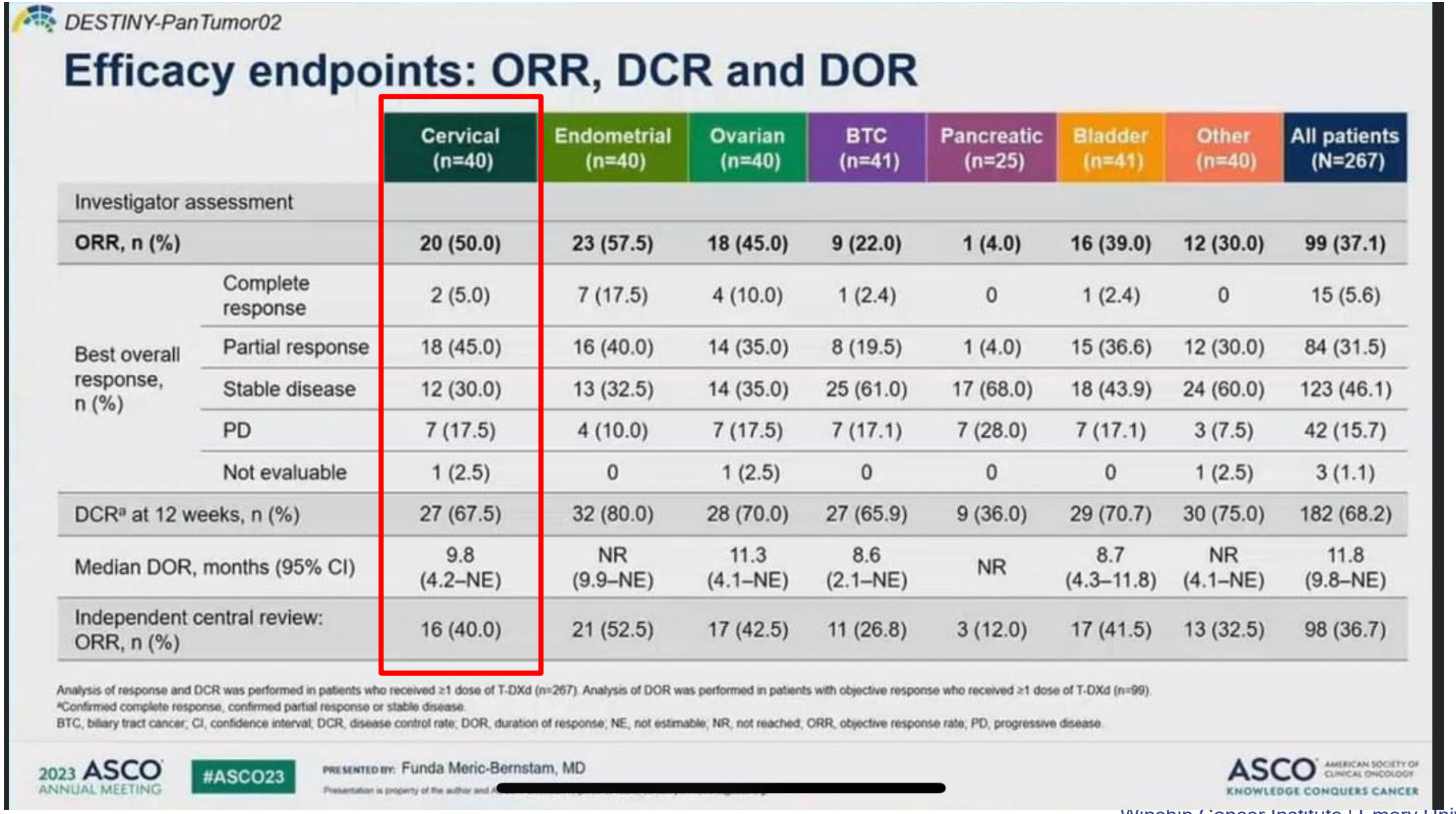
- No contact lenses/irritants
- Cool packs on eyes prior & during infusion
- 3 Drop Regimen
- Lubricating drops Throughout cycle
- Vasoconstriction drops
- 10 min prior
- Corticosteroid drops
- 10 min prior
- Repeat day of infusion 2x
- Day 2-3 tid



ADCs – HER2-directed

- Trastuzumab deruxutecan
- DESTINY 02 Pan Tumor Trial – ASCO2023

Antibody-drug conjugates



DESTINY-PanTumor02

Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Funda Meric-Bernstam, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

The Future?

- PD-1/CTLA4 combination
- AKT inhibitors

Thank you!

Susan C. Modesitt, MD
Leach-Hendee Professor, Gynecologic Oncology, Division Director

Sarah Dilley, MD, MPH
Assistant Professor, Gynecologic Oncology

Chanhee Han, MD
Assistant Professor, Gynecologic Oncology

Namita Khanna, MD
Associate Professor, Gynecologic Oncology

Kristen D. Starbuck, MD
Assistant Professor, Gynecologic Oncology

Lisa Flowers, MD
Professor, Gynecology and Obstetrics (sees patients with precancer/ preinvasive gynecologic disease)