

GARDASIL® Update:
Efficacy Against Intra-Anal Infections and Disease

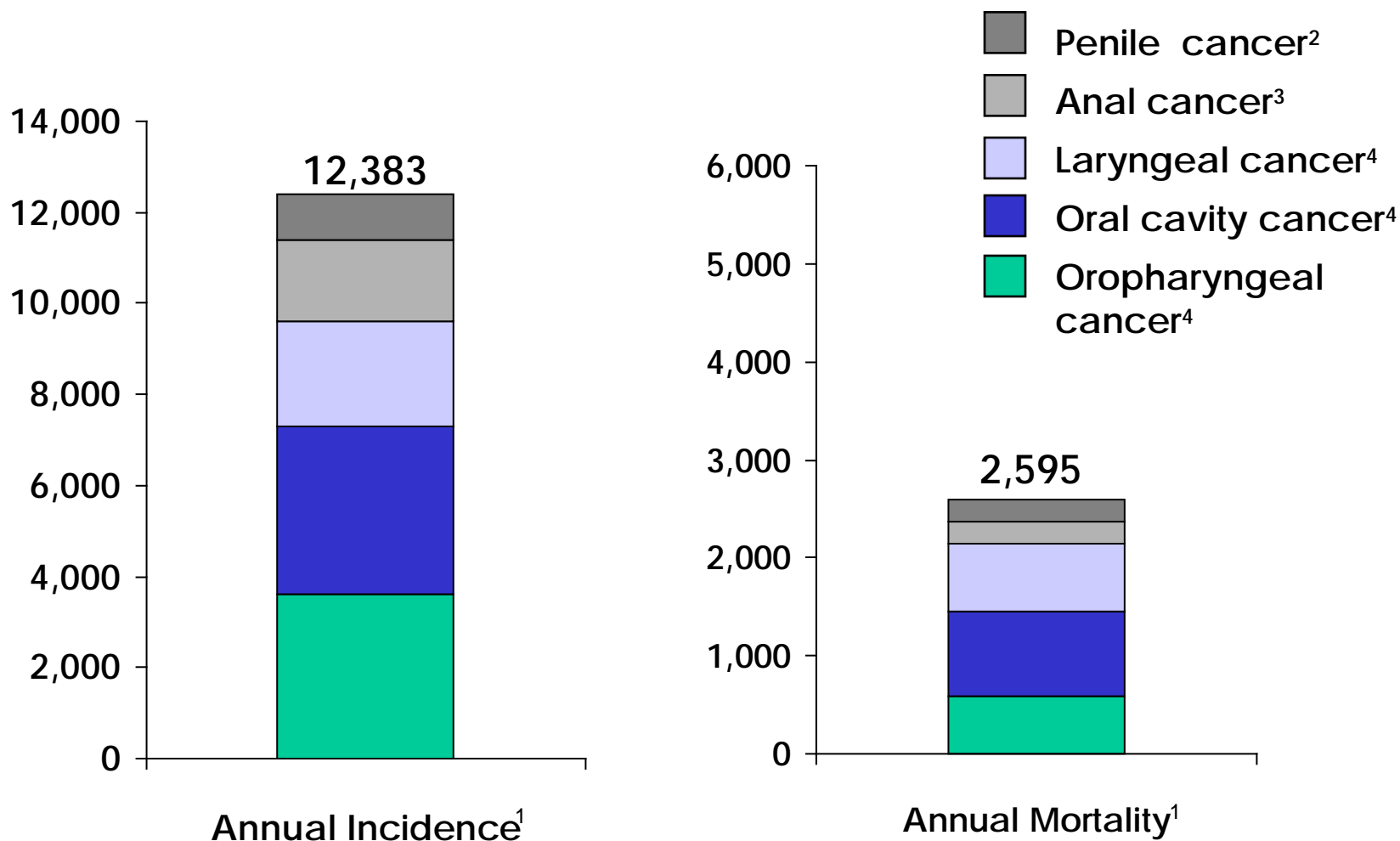
ACIP
February 24, 2010

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Presentation Outline

- HPV disease burden in males
- Protocol 020 overview
- Primary results
 - ❖ Updated EGL efficacy
 - ❖ AIN efficacy
- Safety

Estimated Annual Incidence and Mortality From HPV-Associated Cancers in Males Within the United States

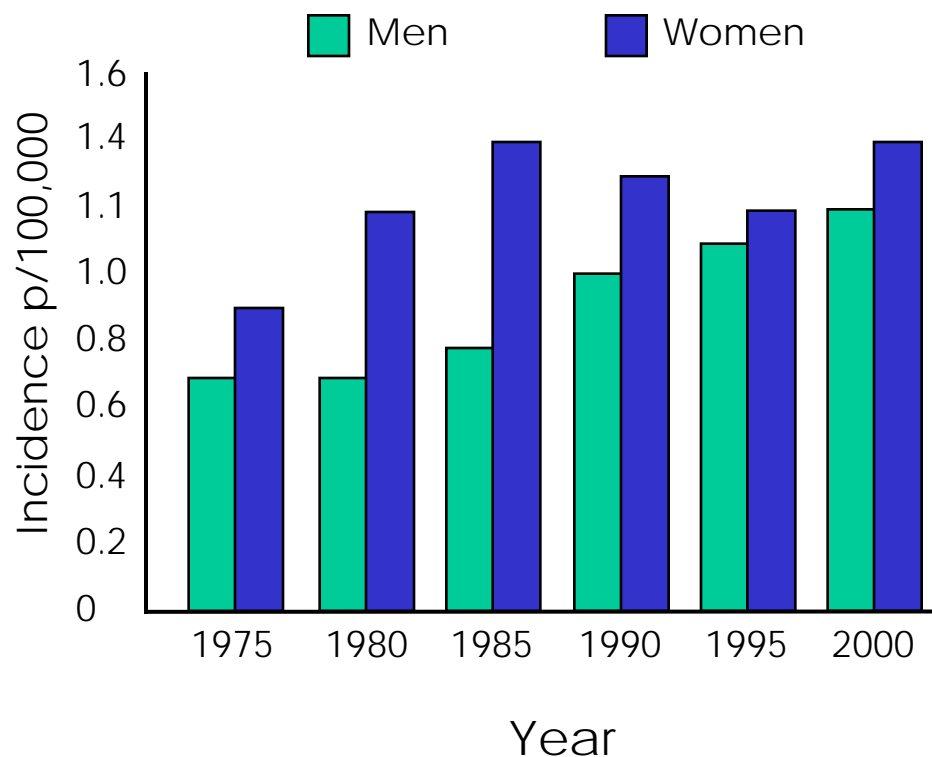


1. Based on American Cancer Society. *Cancer Facts and Figures 2008*. 2. Daling JR et al. *Cancer*. 2004;101:270-280. 3. Ryan DP et al. *N Engl J Med*. 2000;342:792-800. 4. Kreimer AR et al. *Cancer Epidemiol Biomarkers Prev*. 2005;14:467-475.

Anal Cancer Incidence and Association With HPV

- Annual incidence among males in the United States is 2,020¹
- 80% to 90% of cases are HPV related²
- 73% of all tumors associated with HPV 16³
- Incidence of anal cancer is increasing⁴

Incidence of Anal Cancer by Year



1. American Cancer Society. *Cancer Facts and Figures 2008*. 2. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 2007;90. 3. Daling JR et al. *Cancer*. 2004;101:270-280. 4. Partridge JM et al. *Lancet Infect Dis*. 2006;6:21-31.

Protocol 020 Overview & Baseline Analyses

Study Design and Population

- Randomized, double-blind, placebo-controlled, international, multicenter study
- 3 doses of GARDASIL® or placebo at 0/2/6 months
- 36 month follow-up for each subject
- Enrolled subjects:
 - ❖ Heterosexual men (HM)
 - 16-23 year old
 - N=3463
 - ❖ Men having sex with men (MSM)
 - 16-26 year old
 - N=602

Study Design and Population

- Swabs: For HPV DNA testing
 - ❖ Penile
 - ❖ Scrotal
 - ❖ Perineal/perianal
 - ❖ Intra-anal (MSM only)
- Pap smear: For cytology
 - ❖ Intra-anal (MSM only)
- Biopsies: For histology and HPV DNA testing
 - ❖ External genital
 - ❖ Intra-anal (MSM only)

Study Objectives

- Safety: Demonstrate safety and tolerability of GARDASIL™ in young men
- Efficacy: Demonstrate reduction in:
 - ❖ Primary-combined incidence of HPV 6/11/16/18-related
 - External genital lesions (HM + MSM)
 - Intra-anal lesions (MSM only)
 - ❖ Secondary
 - 6/11/16/18 persistent infection
 - Any-time HPV 6/11/16/18 detection
- Immunogenicity: Evaluate vaccine-induced serum anti-HPV 6/11/16/18 responses

Baseline Demographics

Day 1 Vaccine Type HPV Status by Sexual Orientation Group

HPV 6/11/16/18 positive to one or more by	Overall (N=4065)
Serology	7.6
PCR	12.2
PCR or Serology	17.3

Baseline Demographics

Day 1 Vaccine Type HPV Status by Sexual Orientation Group

HPV 6/11/16/18 positive to one or more by	Overall (N=4065)	HM (N=3463)	MSM (N=602)
Serology	7.6	5.0	22.8
PCR	12.2	8.8	30.5
PCR or Serology	17.3	13.3	39.1

HPV 6/11/16/18-Related EGL Efficacy

Per Protocol Efficacy Population

Endpoint	GARDASIL (N=2025)		Placebo (N=2030)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related EGL	1394	3	1404	32	90.6	70, 98

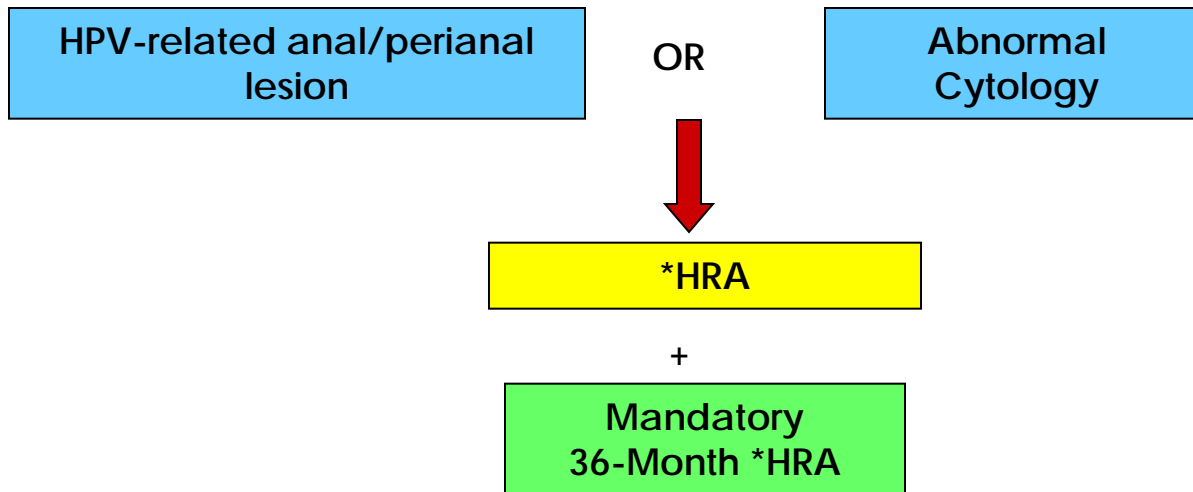
HPV 6/11/16/18-Related EGL Efficacy by Lesion Type

Per Protocol Efficacy Population

Endpoint	GARDASIL (N=2025)		Placebo (N=2030)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related EGL	1394	3	1404	32	90.6	70, 98
Condyloma	1394	3	1404	28	89.3	65, 98
PIN 1 or worse	1394	0	1404	4	100	-52, 100
PIN 1	1394	0	1404	2	100	-435, 100
PIN 2/3 or Cancer	1394	0	1404	2	100	-435, 100
PIN 2/3	1394	0	1404	2	100	-4345, 100
Cancer	1394	0	1404	0	NA	NA

Evaluation of MSM Subjects

- Procedures performed in addition to genital procedures for evaluation of anal endpoints
- Rectal examination at Day 1, Month 7, 12, 18, 24, 30, 36
- Anoscopy if abnormality noted on rectal examination
- Intra-anal swab for HPV PCR at all anogenital examination visits
- Anal cytology



*HRA=High Resolution Anoscopy

MSM Substudy Endpoint

- Endpoint of HPV 6/11/16/18-related AIN or anal cancer met if:

Pathology Panel
consensus diagnosis
of AIN1*, AIN2, AIN3,
Anal Cancer

+

Detection of HPV 6/11/16
or 18 DNA by Thinsection
PCR in an adjacent
section in same tissue
block

*Pathology panel consensus diagnosis of condyloma acuminatum in an intra-anal biopsy specimen are grouped under AIN1 (acuminate and non-acuminate)

HPV 6/11/16/18-Related AIN Efficacy

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)			Placebo (N=299)			Observed Efficacy (%)	95% CI
	n	# Cases	IR/100 PY at Risk	n	# Cases	IR/100 PY at Risk		
HPV 6/11/16/18- Related AIN	194	5	1.3	208	24	5.6	77.5	40, 93

HPV 6/11/16/18-Related AIN Efficacy by Lesion Type

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related AIN	194	5	208	24	77.5	40, 93
AIN 1	194	4	144	16	73.0	16, 93
Condyloma	194	0	144	6	100.0	8, 100
Non-acuminate	194	4	170	11	60.4	-34, 91
AIN 2 or Worse	194	3	208	13	74.9	9, 95
AIN 2	194	2	208	9	75.8	-17, 98
AIN 3	194	2	208	6	63.7	-103, 96
Anal Cancer	194	0	208	0	NA	NA

HPV 16/18-Related AIN 2/3 Efficacy by Lesion Type

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 16/18-Related AIN 2/3	192	1	205	8	86.6	0.013, 100
By HPV Type						
HPV 16	167	1	170	6	82.8	-41, 100
HPV 18	173	0	193	2	100	-501, 100
By Lesion Type						
AIN 2	192	0	205	6	100	9, 100
AIN 3	192	1	205	4	73.0	-173, 100
Anal Cancer	192	0	205	0	NA	NA

Efficacy Against HPV 6/11/16/18-Related Intra-Anal Persistent Infection

MSM Per Protocol Efficacy Population

Endpoint	GARDASIL (N=299)		Placebo (N=299)		Observed Efficacy (%)	95% CI
	n	# Cases	n	# Cases		
HPV 6/11/16/18-Related Intra-Anal Persistent Infection	193	2	208	39	94.9	80, 99
By HPV Type						
HPV 6	140	1	144	13	92.1	47, 100
HPV 11	140	0	144	5	100	-16, 100
HPV 16	166	1	170	16	93.8	60, 100
HPV 18	172	0	193	10	100	52, 100

Safety Data - End of Study

- End of Study safety data consistent with previous data
- SAEs
 - ❖ No new SAEs
 - ❖ 25 SAEs in 21 subjects, none vaccine-related
- Proportion of subjects reporting new medical conditions was comparable between vaccine and placebo groups
 - ❖ 28% vs. 30% (vaccine/placebo)
 - Most common conditions: upper respiratory infections and pharyngitis
- Proportion of subjects reporting conditions potentially consistent with autoimmune phenomena was comparable between vaccine and placebo groups
 - ❖ 0.7% vs. 1.1% (vaccine/placebo)

Conclusions: What does this study indicate?

- High efficacy against 6/11/16/18-related intra-anal persistent infection
- High efficacy against HPV 6/11/16/18-related AIN
- High efficacy against HPV 6/11/16/18-related AIN 2/3
- High efficacy against 16/18-related AIN 2/3



- High efficacy against HPV vaccine type persistent infection and disease (including high-grade) now demonstrated at another anogenital site (CIN, VIN, VaIN, AIN, genital warts)
- High efficacy in both keratinized and mucosal epithelial surfaces in both women and men
 - Pathophysiology of persistent infection of the basal keratinocyte of stratified squamous epithelium is similar regardless of tissue or organ
 - Vaccine efficacy consistent in all tissues studied