

therapy had died as of Dec. 31, 2007, when primary data analysis began. After statistical adjustment for age, socioeconomic status, comorbidity, use of other CYP 2D6 drugs, and timing and duration of tamoxifen therapy, investigators found that the breast cancer mortality risk was increased 24% among women who were coprescribed paroxetine during 25% of their tamoxifen treatment.

If patients took paroxetine longer (that is, for more than half of their tamoxifen course) their breast cancer mortality risk rose to 54%. Patients who took both drugs for 75% of the time they received

tamoxifen had a 91% risk of breast cancer mortality ($P = .0028$).

Mortality from any cause was also sharply elevated among women who took paroxetine for 75% or more of their tamoxifen course ($P = .0027$).

The striking results were significant only for paroxetine, and not for other SSRIs—including fluoxetine, sertraline, fluvoxamine, or citalopram—that were taken concurrently with tamoxifen, reported Dr. Catherine M. Kelly at the meeting.

Dr. Kelly hypothesized that the explanation lies in the degree to which various SSRIs inhibit CYP 2D6. “Paroxetine

is the only SSRI that is an irreversible—or ‘suicide’—inhibitor of CYP 2D6,” she said in an interview.

The dose-response curve of the study, with escalating mortality risk paralleling time on paroxetine, adds significant weight to the findings with regard to paroxetine, marketed as Paxil by GlaxoSmithKline. (The company did not respond to a request for a comment.)

Fluoxetine is also a potent inhibitor of CYP 2D6, but was not shown to increase breast cancer mortality in the study. “I would like to see further data on that and would use caution in using any

of the drugs that inhibit CYP 2D6 in women who are taking tamoxifen, said Dr. Kelly, who was with the University of Toronto Sunnybrook Health Sciences Centre while conducting the study and is currently a breast medical oncology fellow at the University of Texas M.D. Anderson Cancer Center in Houston.

“There are other options,” she noted, including non-SSRI antidepressants that do not inhibit CYP 2D6.

Women need to discuss their choices with a medical oncologist, psychiatrist, or family physician before undergoing tamoxifen therapy, she suggested. ■

New Onset Autoimmune Diseases (NOADs): The pooled safety database, which included controlled and uncontrolled trials which enrolled females 10 through 25 years of age, was searched for new medical conditions indicative of potential new onset autoimmune diseases. Overall, the incidence of potential NOADs, as well as NOADs, in the group receiving CERVARIX was 0.8% (95/12,533) and comparable to the pooled control group (0.8%, 87/10,730) during the 4.3 years of follow-up (mean 3.0 years) (Table 4). In the largest randomized, controlled trial (Study 2) which enrolled females 15 through 25 years of age and which included active surveillance for potential NOADs, the incidence of potential NOADs and NOADs was 0.8% among subjects who received CERVARIX (78/9,319) and 0.8% among subjects who received Hepatitis A Vaccine [720 EL.U. of antigen and 500 mcg Al(OH)₃] control (77/9,325).

Table 4. Incidence of New Medical Conditions Indicative of Potential New Onset Autoimmune Disease and New Onset Autoimmune Disease Throughout the Follow-up Period Regardless of Causality in Females 10 Through 25 Years of Age (Total Vaccinated Cohort)^a

	CERVARIX (N = 12,533) n (%) ^c	Pooled Control Group ^b (N = 10,730) n (%) ^c
Total Number of Subjects With at Least One Medical Condition	95 (0.8)	87 (0.8)
Arthritis ^d	9 (0.0)	4 (0.0)
Celiac disease	2 (0.0)	5 (0.0)
Dermatomyositis	0 (0.0)	1 (0.0)
Diabetes mellitus insulin-dependent (Type 1 or unspecified)	5 (0.0)	5 (0.0)
Erythema nodosum	3 (0.0)	0 (0.0)
Hyperthyroidism ^e	14 (0.1)	15 (0.1)
Hypothyroidism ^f	30 (0.2)	28 (0.3)
Inflammatory bowel disease ^g	8 (0.1)	4 (0.0)
Multiple sclerosis	4 (0.0)	1 (0.0)
Myelitis transverse	1 (0.0)	0 (0.0)
Optic neuritis/Optic neuritis retrobulbar	3 (0.0)	1 (0.0)
Psoriasis ^h	8 (0.1)	11 (0.1)
Raynaud's phenomenon	0 (0.0)	1 (0.0)
Rheumatoid arthritis	4 (0.0)	3 (0.0)
Systemic lupus erythematosus ⁱ	2 (0.0)	3 (0.0)
Thrombocytopenia ^j	1 (0.0)	1 (0.0)
Vasculitis ^k	1 (0.0)	3 (0.0)
Vitiligo	2 (0.0)	2 (0.0)

^a Total vaccinated cohort included subjects with at least one documented dose (N).

^b Pooled Control Group = Hepatitis A Vaccine control group [720 EL.U. of antigen and 500 mcg Al(OH)₃], Hepatitis A Vaccine control group [360 EL.U. of antigen and 250 mcg of Al(OH)₃], and a control containing 500 mcg Al(OH)₃.

^c n (%): number and percentage of subjects with medical condition.

^d Term includes reactive arthritis and arthritis.

^e Term includes Basedow's disease, goiter, and hyperthyroidism.

^f Term includes thyroiditis, autoimmune thyroiditis, and hypothyroidism.

^g Term includes colitis ulcerative, Crohn's disease, proctitis ulcerative, and inflammatory bowel disease.

^h Term includes psoriatic arthropathy, nail psoriasis, guttate psoriasis, and psoriasis.

ⁱ Term includes systemic lupus erythematosus and cutaneous lupus erythematosus.

^j Term includes idiopathic thrombocytopenic purpura and thrombocytopenia.

^k Term includes leukocytoclastic vasculitis and vasculitis.

Serious Adverse Events: In the pooled safety database, inclusive of controlled and uncontrolled studies, which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received CERVARIX and 5.9% (814/13,811) of subjects who received control reported at least one serious adverse event, without regard to causality, during the entire follow-up period (up to 7.4 years). Among females 10 through 25 years of age enrolled in these clinical studies, 6.4% of subjects who received CERVARIX and 7.2% of subjects who received the control reported at least one serious adverse event during the entire follow-up period (up to 7.4 years).

Deaths: In completed and ongoing studies which enrolled 57,323 females 9 through 72 years of age, 37 deaths were reported during the 7.4 years of follow-up: 20 in subjects who received CERVARIX (0.06%, 20/33,623) and 17 in subjects who received control (0.07%, 17/23,700). Causes of death among subjects were consistent with those reported in adolescent and adult female populations. The most common causes of death in the vaccine and control groups were motor vehicle accident and suicide, followed by neoplasm, autoimmune disease, infectious disease, homicide, cardiovascular disorders, and death of unknown cause. Among females 10 through 25 years of age, 31 deaths were reported (0.05%, 16/29,467) of subjects who received CERVARIX and 0.07%, 15/20,192 of subjects who received control.

6.2 Postmarketing Experience: In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for CERVARIX since market introduction (2007) are listed below. This list includes serious events or events which have suspected causal association to CERVARIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination. **Immune System Disorders:** Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, erythema multiforme. **Nervous System Disorders:** Syncope or vasovagal responses to injection (sometimes accompanied by tonic-clonic movements).

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration: There are no data to assess the concomitant use of CERVARIX with other vaccines. Do not mix CERVARIX with any other vaccine in the same syringe or vial. **7.2 Hormonal Contraceptives:** Among 7,693 subjects 15 through 25 years of age in Study 2 (CERVARIX, N = 3,821 or Hepatitis A Vaccine 720 EL.U., N = 3,872) who used hormonal contraceptives for a mean of 2.8 years, the observed efficacy of CERVARIX was similar to that observed among subjects who did not report use of hormonal contraceptives.

7.3 Immunosuppressive Therapies: Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to CERVARIX [see Use in Specific Populations (8.6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Clinical Studies:** Overall Outcomes: In clinical studies, pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued if a subject had a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination. During pre-licensure clinical development, a total of 7,276 pregnancies were reported among 3,696 females receiving CERVARIX and 3,580 females receiving a control (Hepatitis A Vaccine 360 EL.U., Hepatitis A Vaccine 720 EL.U., or 500 mcg Al(OH)₃). The overall proportions of pregnancy outcomes were similar between treatment groups. The majority of women gave birth to normal infants (62.2% and 62.6% of recipients of CERVARIX and control, respectively). Other outcomes included spontaneous abortion (11.0% and 10.8% of recipients of CERVARIX and control, respectively), elective termination (5.8% and 6.1% of recipients of CERVARIX and control, respectively), abnormal infant other than congenital anomaly (2.8% and 3.2% of recipients of CERVARIX and control, respectively), and premature birth (2.0% and 1.7% of recipients of CERVARIX and control, respectively). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported less frequently in 0.1% to 0.8% of pregnancies in both groups. **Outcomes Around Time of Vaccination:** Sub-analyses were conducted to describe pregnancy outcomes in 761 women [N = 396 for CERVARIX and N = 365 pooled control, HAV 360 EL.U., HAV 720 EL.U., and 500 mcg Al(OH)₃] who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose and for whom pregnancy outcome was known. The majority of women gave birth to normal infants (65.2% and 69.3% of recipients of CERVARIX and control, respectively). Spontaneous abortion was reported in a total of 11.7% of subjects (13.6% of recipients of CERVARIX and 9.6% of control recipients) and elective termination was reported in a total of 9.7% of subjects (9.9% of recipients of CERVARIX and 9.6% of control recipients). Abnormal infant other than congenital anomaly was reported in a total of 4.9% of subjects (5.1% of recipients of CERVARIX and 4.7% of control recipients) and premature birth was reported in a total of 2.5% of subjects (2.5% of both groups). Other outcomes (congenital anomaly, stillbirth, ectopic pregnancy, and therapeutic abortion) were reported in 0.3% to 1.8% of pregnancies among recipients of CERVARIX and in 0.3% to 1.4% of pregnancies among control recipients. It is not known whether the observed numerical imbalance in spontaneous abortions in pregnancies which occurred around the time of vaccination is due to a vaccine-related effect. **Pregnancy Registry:** Healthcare providers are encouraged to register pregnant women who inadvertently receive CERVARIX in the GlaxoSmithKline vaccination pregnancy registry by calling 1-888-452-9622. **8.3 Nursing Mothers:** In non-clinical studies in rats, serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via milk during lactation in rats. Excretion of vaccine-induced antibodies in human milk has not been studied for CERVARIX. Because many drugs are excreted in human milk, caution should be exercised when CERVARIX is administered to a nursing woman. **8.4 Pediatric Use:** Safety and effectiveness in pediatric patients younger than 10 years of age have not been established. The safety and effectiveness of CERVARIX have been evaluated in 1,193 subjects 10 through 14 years of age and 6,316 subjects 15 through 17 years of age. [See Adverse Reactions (6.1) and Clinical Studies (14.5) of full prescribing information.] **8.5 Geriatric Use:** Clinical studies of CERVARIX did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. CERVARIX is not approved for use in subjects 65 years of age and older. **8.6 Immunocompromised Individuals:** The immune response to CERVARIX may be diminished in immunocompromised individuals [see Drug Interactions (7.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: CERVARIX has not been evaluated for its carcinogenic or mutagenic potential.

17 PATIENT COUNSELING INFORMATION

Provide the Vaccine Information Statements prior to immunization. This is required by the National Childhood Vaccine Injury Act of 1986 and are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines). Inform the patient, parent, or guardian: Vaccination does not substitute for routine cervical cancer screening. Women who receive CERVARIX should continue to undergo cervical cancer screening per standard of care. CERVARIX does not protect against disease from HPV types to which a woman has previously been exposed through sexual activity. Since syncope has been reported following vaccination in young females, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Information regarding potential benefits and risks associated with vaccination. Report any adverse events to their healthcare provider. Safety has not been established in pregnant women. CERVARIX is not recommended for use in pregnant women or women planning to become pregnant during the vaccination course. Register women who receive CERVARIX while pregnant in the pregnancy registry by calling 1-888-452-9622.

CERVARIX is a registered trademark of GlaxoSmithKline.

Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, US License 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

Full prescribing information for CERVARIX is available at www.cervarix.com.

CRX:1BR5



GlaxoSmithKline
Vaccines

©2010 The GlaxoSmithKline Group of Companies
All rights reserved. Printed in USA. CVX280R0 January 2010

Survival: Breast Conservation vs. Mastectomy

SAN ANTONIO — Breast conservation therapy resulted in significantly better 5-year overall survival, compared with mastectomy, investigators found in a study of 202 patients with triple receptor-negative breast cancer.

Triple receptor-negative breast tumors lack estrogen-, progesterone-, and Her-2/neu-receptor expression. These aggressive cancers account for 15%-20% of the more than 1 million breast cancers diagnosed each year worldwide.

“Despite the aggressive nature [of these tumors], our hypothesis was that breast conservation therapy [might be a] viable option for some patients,” Dr. Catherine C. Parker said at the annual Academic Surgical Congress.

She and her colleagues at Louisiana State University, Shreveport, studied outcomes of 63 patients (31%) who had breast conservation therapy and 139 who received mastectomy. Cancer recurrence rates and survival were the primary outcomes. Mean tumor size at baseline was significantly greater in the mastectomy group, 3.1 cm, versus 2.5 cm in the breast conservation group. A total of 26% of the mastectomy patients had T3 or T4 tumors, compared with 5% of the breast conservation group, a statistically significant difference.

All patients were offered standard of care treatment and surveillance. The mean follow-up was 53 months. Disease-free survival at 5 years was 56% for the mastectomy group and 69% for the breast conservation therapy group. The difference was not statistically significant, Dr. Parker said.

“Five-year overall survival was significantly better for breast conservation therapy [89% vs. 69%],” said Dr. Parker of the department of surgery at LSU.

Reasons for disparity in overall survival include the larger mean tumor size and more advanced stage of disease in the mastectomy group, Dr. Parker said.

Recurrence rates were 30% for the breast conservation group and 43% for the mastectomy group.

A multivariate analysis indicated that the surgical approach had no effect on disease-free or overall survival.

Dr. Parker had no relevant disclosures.

—Damian McNamara