## Nanometastases May Be Tied to Ca Recurrence

## BY BRUCE JANCIN Denver Bureau

SAN ANTONIO — The presence of isolated tumor cells in a sentinel lymph node boosts a breast cancer patient's risk of recurrence or other adverse events 2.5-fold, Dr. Saverio Alberti said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This finding from the largest-ever longterm study of the prognostic significance of isolated tumor cells is at odds with other studies, which have concluded these cells have no significant impact on recurrence, metastasis, or mortality risks.

However, all the negative studies were underpowered and/or included too little follow-up, according to Dr. Alberti of the University of Chieti (Italy). "More than 50% of breast cancer recurrences happen more than 5 years after surgery. So 3- to 4-year studies simply won't do," he added. Dr. Alberti presented a single-institution

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study of 702 consecutive patients with early-stage breast cancer followed for a median of 8.2 years after axillary lymph node dissection. The 377 women with histologically negative sentinel lymph nodes by standard sectioning and hematoxylin and eosin staining had further pathologic analysis. Each of 6,676 lymph nodes removed from patients in this subgroup had 250 sections taken, with each section subjected to both anticytokeratin immunohistochemistry and hematoxylin and eosin staining.

**Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular** Pertussis Vaccine Adsorbed ADACEL™

Brief Summary: Please see package insert for full prescribing information INDICATIONS AND USAGE ADACEL vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria and pertussis as a single dose in persons 11 through 64 years of age. The use of ADACEL vaccine as a primary series, or to complete the primary series, has not been studied. As with any vaccine, ADACEL vaccine may not protect 100% of vaccinated Individuals. CONTRAINDICATIONS Known systemic hypersensitivity to any component of ADACEL vaccine or a life-threatening reaction after previous administration of the vaccine or a vaccine containing the same substances are contraindications to vaccination with ADACEL vaccine. Descuise of uncertainty as to which component of the vaccine may be responsible, additional vaccinations with the diphtheria, tetanus or pertussis components should not be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered. The following events are contraindications to administration of any pertussis containing vaccine: (1)

of any pertussis containing vaccine: (1) • Encephalopathy within 7 days of a previous dose of pertussis containing vaccine not attributable to another identifiable cause. • Progressive encological disorder, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established, the condition has stabilized, and the benefit

clearly outweighs the risk. ADACEL vaccine is not contraindicated for use in individuals with HIV infection. (1)

clearly outweigh the risk. ADACEL vaccine is not contraindicated for use in individuals with HIV infection. (1) WARNINGS Because intramuscular injection can cause injection site hematoma, ADACEL vaccine should not be given to persons with any bleeding disorder, such as hemophila or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits dearly outweigh the risk of administration. If the decision is made to administer ADACEL vaccine in such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection. (1) if any of the following events occurred in temporal relation to previous receipt of a vaccine containing a whole-cell pertussis (eg, DTP) or an acellular pertussis component, the decision to give ADACEL vaccine should be based on careful consideration of the potential benefits and possible risks: (2) (3) • Temperature of B40.5°C (105°F) within 48 hours not due to another identifiable cause; • Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours; • Persistent, inconsolable corging lasting B1 hours, occurring within 48 hours; • Persistent, inconsolable corging lasting B3 hours, occurring within 48 hours; • Veraines with or without fever occurring within 3 days. When a decision is made to withhold pertussis vaccine, Td vaccine should be given. Persons who experienced Arthus-type hypersen-sitivity reactions (eg, severe local reactions associated with systemic symptoms) (4) following a prior dose of tetanus toxoid usually have high nerum tetanus antitoxin levels and should not be given emergency doses of tetanus toxoid-containing vaccines more frequently to individuab with stable central nervous system (CNS) disorders must be made by the health-care provider on an individual bacis, with consideration of all relevant factors and assessment of potential insets and possible risks and benefits for that individual. The ACP has alowed in the relevant exercin or source in a care in a care in

ACIP has published guidelines for vaccination of persons with cereat or acute lines; (1) **PRECAUTIONS General** Do not administer by intravascular injection: ensure that the needle does not penetrate a blood vessel. ADACEL vaccine should not be administered into the buttocks nor by the intradermal route, since these methods of administration have not been studied; a veaker immune response has been observed when these routes of administration have been used with other vaccines. (1) The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (11.1000) and other appropriate agents and equipment should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Prior to administration of ADACEL vaccine, the vaccine recipient and/or the parent or guardian must be asked about personal health history, including immunization history, current health shatus and any adverse event after previous immunizations. In persons who have a history of serious or severe reaction within 48 hours of a previ-ous injection with a vaccine containing similar components, administration of ADACEL vaccine, the vaccine recipient and/or the acid the previous immunizations in persons may be subporting. (1) The immune response to inaCividered vaccines and the vaccine store information of series on the studied. A separate, sterile syringe and nee-die, or a sterile disposable unit, must be used for each person to prevent transmission of bloomer infectious agents. Needles should not be recapped but should be disposed of according boton to prevent transmission of ADACEL vaccine, health-care providers should Area their disposable unit, must be used for each person to prevent transmission of ADACEL vaccine, health-care providers should Area their disposable unit, must be used for each person to prevent transmission of bloob anone infectious agents. Needles should not be recapped but should be tobspoed of according

not be recapped but should be disposed of according to biohazard waste guidelines. Information for Vaccine Recipients and/or Parent or Guardian Before administration of ADACEL vaccine, health-care providers should inform the vaccine recipient and/or parent or guardian of the benefits and risks. The health-care provider should inform the vaccine recipient and/or parent or guardian about the potential for adverse reactions that have been temporally associated with ADACEL vac-cine or other vaccines containing similar components. The vaccine recipient and/or parent or guardian should be instructed to report any serious adverse reactions to their health-care provider. Females of childbearing potential should be informed that Sanofi Pasteur Inc. maintains a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ADACEL vaccine. If they are pregnant or become aware they were pregnant at the time of ADACEL vaccine immunization, they should contact their health-care profes-sional or Sanofi Sasteur Inc. at 1:A00-822-2463 (1 NBO-VACCINE). The health-care provider should provide the Vaccine Information Statements (VISs) that are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting to events required by the VAERS website at http://www.fda.gov/cber/vaers/vaers.htm **Pug Interactions** Immunosuppressive therapies, including inradiation, antimetabolites, alkylating agents, cytotoxic drugs and cor-

Drug Interactions Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and cor-ticosteroids (used in greater than physiologic does), may reduce the immune response to vaccines. (See PRECAUTIONS, Ceneral.) For information regarding simultaneous administration with other vaccines refer to the ADVERSE REACTIONS and DOSAGE AND ticosteroids (used in greater the For information regarding sin ADMINISTRATION sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility No studies have been performed with ADACEL vaccine to evaluate carcino genicity, mutagenic potential, or impairment of fertility.

genicity, mutagenic potential, or impairment of fertility. Pregnany Category C Animal reproduction studies have not been conducted with ADACEL vaccine. It is also not known whether ADACEL vaccine can cause fela harm when administered to a pregnant woman or can affect reproduction capacity. ADACEL vac-cine should be given to a pregnant woman only if clearly needed. Animal fertility studies have not been conducted with ADACEL vaccine. The effect of ADACEL vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental tority studies using pregnant rabbits. Animals were administered ADACEL vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 05 mU/rabbit/occasion (a 17-60 lincreae com-pared to the human dose of ADACEL vaccine on body weight basis), by intramusual rijection. No advese effects on pregna-tions or other evidence of teratogenesis noted in this study. (8) Pregnanzo Registry Health-care movides are encouraged to register orgenant women who rereive ADACEL vaccine in Sanofi Pasteur

Pregnancy Registry Health-care providers are encouraged to register pregnant women who receive ADACEL vaccine in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463 (1-800-VACCINE).

Nursing Mothers It is not known whether ADACEL vaccine is excreted in human milk. Because many drugs are excreted in human milk, aution should be exercised when ADACEL vaccine is given to a nursing woman. Pediatric Use ADACEL vaccine is not indicated for individuals less than 11 years of age. (See INDICATIONS AND USAGE.) For immu-nization of persons 6 weeks through 6 years of age against diphthenia, tefanus and perfussis refer to manufacturers' package inserts

for DTate Vaccines. Geriatric Use ADACEL vaccine is not indicated for individuals 65 years of age and older. No data are available regarding the safety and effectiveness of ADACEL vaccine in individuals 65 years of age and older as clinical studies of ADACEL vaccine did not include subjects in the geriatric population. ADVERSE REACTIONS The safety of ADACEL vaccine was evaluated in 4 clinical studies. A total of 5,841 individuals 11-64 years of age inclusive 3,333 dolescent 11-17 years of age and 2,448 adults 18-64 years) received a single booster dose of ADACEL vaccine. The principal safety study was a randomized, observer blind, active controlled trial that enrolled participants 11-17 years of age (ADACEL vaccine N = 1,184; Td vaccine N = 792) and 18-64 years) received a single booster dose of ADACEL vaccine N = 573). Study participants had not received tetanus or dipitheria containing vaccines within the previous 5 years. Observer blind design, ie, study per-sonnel collecting the safety data differed from personnel administering the vaccines, was used due to different vaccine packaging (ADA-

Product information as of January 2006

Manufactured by: Sanofi Pasteur Limited Toronto Ontario Canada

MKT10383-1R

CEL vaccine supplied in single dose vials; Td vaccine supplied in multi-dose vials). Solicited local and systemic reactions and unsolicited events were monitored daily for 14 days post-vaccination using a dary card. From days 14-28 post-vaccination, information on adverse events necessitating a medical contact, such as a telephone call, visit to an emergency room, physician's office or hospitalization, was obtained via telephone interview or at an interim clinic visit. From days 28 to 6 months post-vaccination, participants were monitored for unexpected visits to a physican's office or to an emergency room, onset of serious ilness and hospitalization. Telepatine adverse events that occurred in the 6 month post-vaccination time period was obtained via a scripted telephone interview. Approximately 96% of participants ompleted the 6-month follow-up evaluation. In the concomitant vaccination study with ADACEL and Hepatitis B vaccines, local and systemic adverse events were monitored daily for 14 days post-vaccination in adverse events were only monitored at site/arm of ADACEL vaccine administration. Unsolicited earcitors (including immediate reac-tions, serious adverse events and events that elicited seeking medical attention) were collected at a diric visit or via telephone interview for the duration of the trial, jue up to six months post-vaccination. In the concomitant vaccination sing a diary card. All unsolited reactions occurring through day 14 were collected. From day 14 to the end of the trial, jue up to 24 days, only events that elicited seeking medical attention were collected. In all studies jubjects were monitored for relation subserved in the rates observed in rate at dist of avacine cannot be directly compared to rates in the dinical trials of anderse reaction rates observed in rate at the study. Because clinical trials are conducted under widely varying conditions, adverse events that appear to be related to vaccine use and for approximating rates of those events. **Serious Adverse Eve** 

in the other trials and there were no additional neuropathic events reported. Solicited Adverse Events in the Principal Safety Study The frequency of selected solicited adverse events (erythema, swelling, pain and freer) occurring during Days 0-14 following one dose of ADACE vaccine or Td vaccine were reported at a similar frequency in both groups. Few participants (<1%) sought medical attention for these reactions. Pain at the injection site was the most common adverse reaction occurring in 62-78% of all vaccinese. In addition, overall rates of pain were higher in adolescent solitone reopients ATA attes of moderate and severe pain in adolescent soliton to significantly differ for adults. Fever of 38°C and higher was uncommon, although in the ado-lescent age group, it occurred significantly more frequently in ADACEL vaccine recipients than Td vaccine recipients. Bit (B) The rates of vaccination period. Most local reactions occurred within the first 3 days after vaccination (with a mean duration of less than 3 days). Headache was the most frequent systemic reaction and was usually of mild to moderate intensity. Adverse Events in the Concomitant Vaccine Studies

Adverse Events in the Concomitant Vaccine Studies Local and Systemic Reactions when Given with Hepatitis B Vaccine The rates reported for fever and injection site pain (at the ADA-CEL vaccine administration site) were similar when ADACEL and Hep B vaccines were given concurrently or separately. However, the rates of injection site enthman (23.4% for concomitant vaccination and 21.4% for separate administration) and swelling (23.9% for concomitant vaccination and 17.9% for separate administration) at the ADACEL vaccine administration site were increased when co-administred. Swollen and/or sore joints were reported by 22.5%, for concomitant vaccination and 7.9% for separate administra-tion. The rates of generalized body aches in the individuals who reported swollen and/or sore joints were 86.7% for concomitant vac-cination and 72.2% for separate administration. Most joint complaints were mild in intensity with a mean duration of 1.8 days. The incidence of other solicited and unsolicited adverse events were not different between the 2 study groups. (8)

Inductive to other solucter and unsolucit adverse events were not unterest to the 2 study groups, (6) Local and systemic Reactions when Grew with Trivatent Inactivated Influenza Vaccime The rates of fever and injection site erythe-ma and swelling were similar for recipients of concurrent and separate administration of ADACEL vaccine and TV. However, pain at the ADACEL vaccine injection site occurred at statistically higher rates following concurrent administration (66.6%) versus separate administration (06.0%). The rates of sore and/or sovellen joints were 13% for concurrent administration and 9% for separate admin-istration. Most joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unso-licited advectors the paratety between the other sources. licited adverse events were similar between the 2 study groups. (8)

administration (60.8%). The rates of sore and/or swollen joints were 13% for concurrent administration and 9% tor separate admin-stration. Mox joint complaints were mild in intensity with a mean duration of 2.0 days. The incidence of other solicited and unso-licited adverse events were similar between the 2 study groups. (8) Additional Studies An additional 1,806 adolescents received ADACEL vaccine as part of the lot consistency study used to support ADACEL vaccine licensure. This study was a randomized, double-blind, multi-center trial designed to assess lot consistency as meas-ured by the safety and immunogenicity of 3 lots of ADACEL vaccine when given as a booster dose to adolescents 11-17 years of age inclusive. Local and systemic adverse events were monitored for 14 days post-vaccination using a diary card. Unsolited adverse event occurring in approximately 80% of all subjects. Headache was the most frequently reported systemic event occurring in approx-imately 44% of al subjects. Sore and/or swollen joints were reported by approximately 14% of participants. Most joint complaints were mild in intensity with a mean duration of 2.0 days, (8) An additional 952 adolescents and adults received DACEL vaccine intere supports canadian studies used as the basis for licensure in other countries. Within these clinical triak, the rates of local and systemic reactions following ADACEL vaccine were similar to those reported in the four principal triaks in the US with the exception of a higher rate (86%) of adults experiencing 'any' local injection site pain. The rate of severe pain (0.8%), however, was compara-ble to the rates reported in the four principal triak. (8) There was one spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous report of whole-arm swelling of the injected limb among the 277 Td vaccine recipients, and two spontaneous report of whole-arm swelling of the injected limb among the routines, Because these events are reported voluntari

Department, asion reaction that, postering briefs, primitizing r a toxif or an indeparted (ProcerveCartic). DOSAGE AND ADMINISTRATION ADACEL vaccine should be administered as a single injection of one dose (0.5 mL) by the intra-muscular route. SHAKE THE VIAL WELL to distribute the suspension uniformly before withdrawing the 0.5 mL dose for administra-tion. Five years should have elapsed aince the recipient's last dose of teaturus toxidi, diphtheria toxoid and/or perfussis containing vac-cine. Do NOT administer this product intravenously or subcutaneously. STORAGE Store at 2° to 8°C (35° - 46°F). DO NOT FREEZE. Discard product if exposed to freezing. Do not use after

expiration date. **REFERENCES 1.** CDC, General recommendations on immunization: recommendations of the Advisory Committee on Immunization **Practices** (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR-2):135. 2. CDC. Pertussis vaccina-tion: Use of acellular pertussis vaccines among infants and young children. Recommendations of the ACIP. MMWR 1997;46(RR-7):1-25. 3. CDC Update. Vaccine side effects, adverse reactions, contraindications and precautions - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR-12):1-35. 4. CDC. Update on adult immunization: recommendations of the Advisory Committee (ACIP). MMWR 1996;45(RR-12):1-35. 4. CDC. Update on adult immunization: recommendations of the Advisory Committee (ACIP). MMWR 1991;40(RR-10):1-28. 6. CDC. Use of vaccines and immune globu-lins in persons with altered immunocompetence. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1993;42(RR-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):0-18. 2. CDC. Update Vaccine adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):0-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):1-18. 7. CDC. Current trends - Vaccine Adverse Event Reporting System (VAERS) United States. MMWR 1990;39(4):73(-R-4):1-18. 7. CDC. Current trends - National Vaccine injury act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37(13):197-200. 10. FDA. New reporting re

Printed in Canada

Distributed by: **Sanofi Pasteur Inc.** Swiftwater PA 18370 USA R1-0106

Of the 377 patients, 13% had nodes containing isolated tumor cells not more than 0.2 mm in diameter, which Dr. Alberti calls nanometastases. The risk of local recurrence, contralateral breast cancer. or distant metastasis at 8 years in patients with nanometastases was 2.5-fold greater than in patients who were truly node negative. Event rates were closely similar in the two groups until 36 months, at which point they diverged sharply, he said.

The risk associated with nanometastases was similar to that with micrometastases 0.2-2.0 mm in size in the Italian study. American Society of Clinical Oncology guidelines recommend routine axillary node dissection for patients with micrometastases on sentinel node biopsy.

Dr. Alberti foresees that the best use of nanometastases as a prognostic indicator would be to incorporate them as one of the factors employed in the nomogram developed at Memorial Sloan-Kettering in New York for use in assessing which sen-



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DR. ALBERTI

tinel node-positive patients should receive a complete axillary dissection. The nomogram, based on eight characteristics of the primary tumor and sentinel node lesion, is gaining use in clinical decision making (Ann. Surg. Oncol. 2003;10:1140-51).

In a separate presentation, Dr. Emiel Rutgers of the Netherlands Cancer Institute, Amsterdam, argued that at present the finding of nanometastases in a sentinel node has no clinical relevance and affected patients should be classified as node negative.

He cited a Dutch retrospective study involving 2,150 patients with early breast cancer who underwent sentinel lymph node biopsy. The prevalence of nanometastases in the sentinel node was 4.9%. Fewer than 8% of patients who were sentinel node positive for nanometastases had additional metastases in other nodes. The result was upstaging of 4% of the patients, with no recommended change in anyone's treatment. Therefore, the benefits of doing an intensive search for isolated tumor cells are questionable, Dr. Rutgers said.

He added that recent evidence indicates not all immunohistochemistry-positive cells in the sentinel node are viable isolated tumor cells. Some are iatrogenically displaced normal epithelial cells (J. Clin. Oncol. 2006;24:2013-8).

The goal of research involving nanoand micrometastases is to develop a means of identifying the 15% of patients with early-stage breast cancer who will relapse. This would enable the other 85% to be spared unnecessary adjuvant systemic therapy. In Dr. Rutgers' view, a more promising approach than the labor-intensive search for nanometastases of as-yet unproven prognostic value involves predictive gene array tests.