

Femara Downstaged Tumors to Operable Size

BY DAMIAN McNAMARA

PALM BEACH, FLA. — Neoadjuvant aromatase inhibitor therapy allows some breast cancer patients to be downstaged to breast-conserving surgery rather than being considered inoperable or as candidates for mastectomy, according to results of a multicenter phase II trial.

The treatment shrank tumors from a median 4.9 cm to 3.0 cm for a “highly sig-

nificant difference preoperatively versus after therapy,” said Dr. George S. Leight Jr., a general surgeon at Duke University Medical Center, Durham, N.C.

Because experience with neoadjuvant aromatase inhibitor therapy is limited in the United States, Dr. Leight said, he and his associates studied 106 postmenopausal women who either had inoperable breast cancer or had been recommended for mastectomy. The women

had estrogen receptor–positive, stage II/III breast cancer and palpable tumors of 2 cm or larger.

Seven women chose neoadjuvant chemotherapy and three declined surgery, so researchers assessed surgical outcomes for the remaining 96 women. Participants were treated with the aromatase inhibitor letrozole (Femara) for 16-24 weeks.

In all, 48 of the women had successful

breast-conserving operations. Women in this arm included 30 of 46 patients who were initially identified as likely to require a mastectomy, as well as 15 of 39 patients who were initially judged to definitely require a mastectomy. Results were presented at the annual meeting of the Southern Surgical Association.

“This is an excellent study,” said Dr. Kelly K. Hunt, chief of the surgical breast section in the department of surgical oncology at the University of Texas M.D. Anderson Cancer Center, Houston. “The fact that they could downstage patients to more surgical options, especially breast-conserving surgery, is important.”

The 11 women who had been deemed inoperable at baseline were converted to operable status, including 3 who had successful breast-conserving surgery.

Dr. Leight, lead author John A. Olson Jr., and their associates gauged clinical response with ultrasound and/or mammography. In all, 13% of women had a complete response to aromatase inhibitor therapy, 49% had a partial response, 26% had stable disease, and the remaining 12% had progressive breast cancer.

“Do you think other imaging studies, such as MRI or PET scan, would be more appropriate than ultrasound?” Dr. Hunt asked.

“Regarding imaging, the inadequacy of mammograms and ultrasound is clear,” said Dr. Olson, chief of endocrine, breast, and oncologic surgery at Duke. “MRI and PET are options, but [are] full of limitations that are not addressed in this trial.”

The remaining 48 women still had mastectomy. “The decision between mastectomy and breast-conserving surgery is complex, and we were sobered by the number of patients who had very small tumors yet still had mastectomy,” Dr. Olson said.

Pretreatment T stages were T2 in 53% of patients, T3 in 37%, and T4 in 10%. Following treatment with letrozole, T stages changed to T0 in 1%, T1 in 41%, T2 in 41%, T3 in 13%, and T4 in 4%.

“This suggests that a significant number of patients who had mastectomy could have had breast-conserving surgery,” Dr. Leight said.

“I assume most of these patients with median tumor size of 5 cm are going to get chemotherapy anyway. What is the rationale for giving endocrine therapy up front instead of chemotherapy?” asked Dr. Kelly M. McMasters, chair of the surgery department at the University of Louisville (Ky.).

“Regarding a 5-cm tumor being treated with endocrine therapy versus chemotherapy—that is the point—it is appropriate to treat large, estrogen receptor–rich tumors with endocrine therapy,” Dr. Olson said.

Neither Dr. Leight nor Dr. Olson had any relevant financial disclosures.

The trial was sponsored by the National Cancer Institute. ■

ALDARA® (imiquimod) Cream, 5%

Brief Summary of External Genital Wart Prescribing Information See Package Insert for Full Prescribing Information

INDICATIONS AND USAGE: External Genital Warts: Aldara Cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older. **Unevaluated Populations:** The safety and efficacy of Aldara Cream in immunosuppressed patients have not been established. Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions. Efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Local Inflammatory Reactions: Intense local inflammatory reactions including skin weeping or erosion can occur after few applications of Aldara Cream and may require an interruption of dosing. Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Administration of Aldara Cream is not recommended until the skin is completely healed from any previous drug or surgical treatment. **Systemic Reactions:** Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered. **Ultraviolet Light Exposure:** Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g., a hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Aldara Cream. Aldara Cream shortened the time to skin tumor formation in an animal phototoxicity study. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure. **Unevaluated Uses: External Genital Warts:** Aldara Cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease.

ADVERSE REACTIONS: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience: External Genital Warts:** In controlled clinical trials for genital warts, the most frequently reported adverse reactions were local skin and application site reactions. Some subjects also reported systemic reactions. Overall, 1.2% (4/327) of the subjects discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

Table 1: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (External Genital Warts)

	Aldara Cream		Vehicle	
	Females n=114	Males n=156	Females n=99	Males n=157
	All Grades* Severe	All Grades* Severe	All Grades* Severe	All Grades* Severe
Erythema	74 (65%) 4 (4%)	90 (58%) 6 (4%)	21 (21%) 0 (0%)	34 (22%) 0 (0%)
Erosion	35 (31%) 1 (1%)	47 (30%) 2 (1%)	8 (8%) 0 (0%)	10 (6%) 0 (0%)
Excoriation/ Flaking	21 (18%) 0 (0%)	40 (26%) 1 (1%)	8 (8%) 0 (0%)	12 (8%) 0 (0%)
Edema	20 (18%) 1 (1%)	19 (12%) 0 (0%)	5 (5%) 0 (0%)	1 (1%) 0 (0%)
Scabbing	4 (4%) 0 (0%)	20 (13%) 0 (0%)	0 (0%) 0 (0%)	4 (3%) 0 (0%)
Induration	6 (5%) 0 (0%)	11 (7%) 0 (0%)	2 (2%) 0 (0%)	3 (2%) 0 (0%)
Ulceration	9 (8%) 3 (3%)	7 (4%) 0 (0%)	1 (1%) 0 (0%)	1 (1%) 0 (0%)
Vesicles	3 (3%) 0 (0%)	3 (2%) 0 (0%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)

*Mild, Moderate, or Severe

Remote site skin reactions were also reported. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%). Selected adverse reactions judged to be probably or possibly related to Aldara Cream are listed below.

Table 2: Selected Treatment Related Reactions (External Genital Warts)

	Females		Males	
	Aldara Cream n=117	Vehicle n=103	Aldara Cream n=156	Vehicle n=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	38 (32%)	21 (20%)	34 (22%)	16 (10%)
Burning	30 (26%)	12 (12%)	14 (9%)	8 (5%)
Pain	9 (8%)	2 (2%)	3 (2%)	1 (1%)
Soreness	3 (3%)	0 (0%)	0 (0%)	1 (1%)
Fungal Infection*	13 (11%)	3 (3%)	3 (2%)	1 (1%)
Systemic Reactions:				
Headache	5 (4%)	3 (3%)	8 (5%)	3 (2%)
Influenza-like symptoms	4 (3%)	2 (2%)	2 (1%)	0 (0%)
Myalgia	1 (1%)	0 (0%)	2 (1%)	1 (1%)

*Incidence reported without regard to causality with Aldara Cream.

Adverse reactions judged to be possibly or probably related to Aldara Cream and reported by more than 1% of subjects included: **Application Site Disorders:** burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness. **Remote Site Reactions:** bleeding, burning, itching, pain, tenderness, tinea cruris. **Body as a Whole:** fatigue, fever, influenza-like symptoms. **Central and Peripheral Nervous System Disorders:** headache. **Gastro-Intestinal System Disorders:** diarrhea. **Musculo-Skeletal System Disorders:** myalgia. **Clinical Trials Experience: Dermal Safety Studies** Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that Aldara Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and application site reactions were reported in the clinical studies. **Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of Aldara Cream. Because these reactions 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

drug exposure. **Body as a Whole:** angioedema. **Cardiovascular:** capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope. **Endocrine:** thyroiditis. **Hematological:** decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma. **Hepatic:** abnormal liver function. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis, erythema multiforme, hyperpigmentation. **Vascular:** Henoch-Schönlein purpura syndrome.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (577X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons). Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons). A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons). There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are excreted in human milk, caution should be exercised when Aldara Cream is administered to nursing women. **Pediatric Use:** Safety and efficacy in patients with external genital/perianal warts below the age of 12 years have not been established. Aldara Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Aldara; median age 5 years, range 2-12 years). Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. These studies failed to demonstrate efficacy. Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with MC was application site reaction. Adverse events which occurred more frequently in Aldara-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara vs. 2% vehicle). Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Aldara-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subjects' weight. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/L. **Geriatric Use:** Of the 215 subjects treated with Aldara Cream in the actinic keratosis clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Aldara Cream in the superficial basal cell carcinoma clinical studies, 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE: Topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

CLINICAL STUDIES: In a double-blind, placebo-controlled clinical study, 209 otherwise healthy subjects 18 years of age and older with genital/perianal warts were treated with Aldara Cream or vehicle control 3 times per week for a maximum of 16 weeks. The median baseline wart area was 69 mm² (range 8 to 5525 mm²). Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

Table 14: Complete Clearance Rates (External Genital Warts)- Study EGW1

Treatment	Subjects with Complete Clearance of Warts		Subjects with Warts Remaining at Week 16	
	Subjects Without Follow-up	Subjects with Warts Remaining at Week 16	Subjects Without Follow-up	Subjects with Warts Remaining at Week 16
Overall	54 (50%)	19 (17%)	36 (33%)	62 (62%)
Aldara Cream (n=109)	11 (11%)	27 (27%)	62 (62%)	
Vehicle (n=100)				
Females				
Aldara Cream (n=46)	33 (72%)	5 (11%)	8 (17%)	19 (48%)
Vehicle (n=40)	8 (20%)	13 (33%)	19 (48%)	
Males				
Aldara Cream (n=63)	21 (33%)	14 (22%)	28 (44%)	43 (72%)
Vehicle (n=60)	3 (5%)	14 (23%)	43 (72%)	

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