# Controlling Breast Cancer

*a report by*
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The current National Cancer Institute (NCI) director's goal—to eliminate death and suffering from cancer by 2015—is laudable but naïve and impractical, given the immensity of the task and the tools at hand. Only three cancer-fighting strategies exist—treatment, screening, and prevention. Focussing on breast cancer, one can examine current achievements and generate a 10-year forecast, based on likely new developments. Potential barriers and costs will be estimated.

## Treatment

Prospects have improved with the development of new drugs that interfere with unique biochemical pathways driven by cancer-causing mutations. The translation of molecular findings into practical treatments is exemplified by the recent approval and acceptance of Herceptin® in clinical practice. This antibody targets the cell surface marker for a particularly lethal subtype of breast cancer, and is active only in patients carrying that marker. Identifying patients likely to benefit was a major challenge, solved by rigorous testing of large populations in early clinical trials. Recent randomized studies prove that carefully selected patients enjoy markedly improved outcomes if Herceptin is combined with standard chemotherapy at the time of original diagnosis. Other new US Food and Drug Administration (FDA)-approved biologic agents, (Avastin®, Tarceva®, and Erbitux®) cannot be prescribed with confidence (or insurance coverage) until the logistical hurdles of patient selection and definition of optimal combinations are solved. Similarly, investigational agents such as sorafenib and lapatinib are poised for approval but will not be used widely until the same barriers are breached.

Another area of hot research is the genotyping of cancer cells to determine whether a patient will or will not benefit from specific treatments, including standard hormone or chemotherapy, or new biologics. In particular, the OncotypeDX® assay of 21 cancer-related genes predicts patient outcome, and can guide the drug therapy of post-menopausal women at the time of initial diagnosis. In a perfect future, effective therapies will cure rather than palliate, and they will be used only on those patients who will benefit from them. This is known as the testicular cancer paradigm—treatment can cure, even if used in advanced disease. Currently, medical treatments extend the lives of breast cancer patients by approximately five years beyond that expected with only surgery or radiation. New treatments will buy even more survival time, but no cures are on the horizon. Side effects of current cancer therapies range from none to debilitating, and individual patient costs can exceed US$100,000 per year.

## Screening

Screening is widely accepted, despite remaining doubts about overall benefit and cost-effectiveness. Strong opinions promote its use, based on the assumption that cancers discovered early can be excised and cured. Randomized trials encompassing half a million women have the statistical power to demonstrate a relative benefit for screened versus unscreened women. However, in absolute terms, only six per 10,000 women benefit from regular screening, whereas several thousand will undergo additional tests and biopsies. A recent comparison of women diagnosed with either early or advanced breast cancers found that similar proportions had participated in screening.

The notion that 'timely surgery can cure' is becoming outdated as it ignores two important bodies of knowledge. Firstly, most screen-detected breast cancers are slow-growing, with a low likelihood for harm. Finding and excising these low-risk cancers, many of which are destined to remain dormant, makes only a small impact in overall cancer mortality, while committing a large number of women to treatment. In addition, pre-cancerous tissue, which is often found via screening, is frequently over-treated, as a clear consensus on optimal management is lacking. Ironically, screened populations have approximately 50% more breast cancers than unscreened populations, because screening detects so many low-risk cases that would never become clinically significant. Consequently, many healthy women are labeled cancer patients. Meanwhile, the most lethal cancers are often missed by screening mammograms either because they cannot be differentiated from surrounding normal tissue, or because they grow quickly in the interval between screening examinations. Despite the promise of digital

mammography, it has not been proven to be better than standard technology. A screening test that preferentially finds lethal cancers is needed.

The second area of research arguing against a strategy of early detection is the discovery that breast cancer cells often disperse early in the course of the disease. With new pathologic technologies, they can be seen in the bloodstream, lymph nodes (LNs), bone marrow and elsewhere, even in women thought to be cured by surgery. Whether the cells remain dormant for decades, or grow rapidly, the cat is out of the bag. Early detection, to accomplish a surgical cure, will probably not work. These cases need medication that works throughout the entire body, to suppress or eliminate the disseminated cells.

Societally, population-based screening is now being committed to, despite the associated burdens of downstream testing, over-diagnosis, and over-treatment. No significant improvements in mammography are on the horizon, although alternative screening tests (magnetic resonance imaging (MRI), ultrasound, and ductal lavage) are being evaluated. Current costs are very high, estimated to be several hundred dollars per woman per year, for every woman who chooses to be screened.

## Prevention

Ideally, prevention would be the best solution. Breast cancer is caused by multiple mutations in normal breast tissue, and preferential growth of those mutated cells. Mutations can be congenital, like inherited breast cancer mutations, or acquired, with ionizing radiation the only proven culprit. Growth of breast tissue, normal or abnormal, is stimulated by hormones and perhaps by other growth factors as well. If a woman is born with a breast cancer gene mutation, she can consider prophylactic mastectomies or hormone suppression, via removal of the ovaries or anti-hormone medications. Women at high risk for breast cancer because of prior radiotherapy for childhood cancer or lymphoma can reduce their risk by the same means. These circumstances are rare, but they offer insight into prevention strategies for the more common, sporadic breast cancers.

Regardless of causation, the mutations that lead to breast cancers accumulate during a woman's lifetime. Older women are therefore much more likely to develop breast cancer than younger women. Besides age, factors that increase risk are those associated with increased exposure to uninterrupted estrogen—early menarche, late pregnancies, low parity, late menopause, and supplemental hormones. Until recently, the negative impact of post-menopausal hormones was underestimated and thought to be a fair trade-off for their presumed cardiac benefits. However, results from the Women's Health Initiative (WHI) were reported in 2002. Post-menopausal women were randomized to receive hormone therapy or placebo, with a primary end-point of cardiac disease. The study was stopped early because of an increased incidence of cardiac and thrombo-embolic events, as well as breast cancer, in women receiving both estrogen and progesterone.

In the UK, the Million Women Study (MWS) obtained detailed information about the use of hormone replacement therapy (HRT), and confirmed the findings of the WHI. These studies resulted in most public health advisory committees withdrawing their previous recommendations for menopausal hormone therapy. Interestingly, when the study drugs were stopped abruptly in the WHI, 67% of women receiving hormones, and 40% of women receiving placebo experienced moderate or severe side effects, demonstrating the suggestibility of health-conscious women and their beliefs about the subjective benefits of hormone therapy. It is interesting to speculate how much the use of post-menopausal hormones has contributed to the increasing incidence of breast cancer over the past 25 years.

*The inadequately studied neurologic effects of AIs could limit their use as cancer prevention agents where the tolerance for side effects is low; however, benefits and risks must be weighed up.*

Besides avoiding cancer-promoting hormones, a woman can take medications to reduce the hormone stimulation of her breasts. Two classes of anti-cancer hormones exist—selective estrogen receptor modifiers, (SERMs), which include tamoxifen (Nolvadex®) and raloxifene (Evista®), and Aromatase inhibitors (AIs), which include anastrazole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®).

For 40 years, the SERM tamoxifen has been a mainstay in the treatment of metastatic breast cancer and as adjuvant therapy to prevent recurrence after surgery for 25 years. It only works in hormone-sensitive breast cancers, which comprise approximately two-thirds of all breast cancers. Tamoxifen and another SERM (raloxifene) have been proven to prevent one-half of new breast cancers in women at moderate to high risk. Pre-cancers are also reduced. These drugs affect all bodily tissues influenced by estrogen. Like estrogen, they improve bone mineral density (BMD), cause blood clots, and stimulate proliferation of the uterine lining, even leading to cancer. However, they have an anti-estrogen effect on the breast, decreasing tissue density and reversing proliferative activity, and they cause hot flashes.

AIs are a new class of drugs for hormone-sensitive breast cancer. These drugs block the estrogen-producing enzyme aromatase and are effective against metastatic breast cancer resistant to SERMs. More recently they have been recommended for adjuvant treatment to prevent recurrence after initial breast cancer surgery—in this context they are roughly equivalent to SERMs in reducing cancer mortality. The AI side effect profile is attractive—no blood clots or uterine cancer, and fewer hot flashes; however, they may weaken bones, and women have more fractures. Bone-strengthening drugs can reverse the AI effect on BMD, but they do not prevent the increased risk of falling, also seen with AIs. Impaired cognition has also been documented.

The inadequately studied neurologic effects of AIs could limit their use as cancer prevention agents where the tolerance for side effects is low; however, benefits and risks must be weighed up. These drugs appear to prevent breast cancer very effectively. Testing of AIs versus SERMs in women with newly diagnosed breast cancer reveals a greater reduction in new breast cancers with AIs. This finding has led to several small AI prevention trials in the US, targeting women at high risk because of increased breast density or high serum estrogen levels. In addition, two large randomized controlled trials, each accruing several thousand post-menopausal women, are also under way. An international trial sponsored by Pfizer compares exemestane with placebo, with early results anticipated in 2010. A similar trial, sponsored by AstraZeneca in the UK, compares anastrazole with placebo.

These trials are extremely likely to yield positive results, and widespread adoption by women at moderate or high risk could reduce breast cancer incidence by 50%. Ultimately, the acceptance of these drugs will depend on their side effects and price, which currently stands at more than US$100 per month. By contrast, tamoxifen has just lost patent protection and is inexpensive (under US$10 per month), but is still not widely used for cancer prevention because of the potential side effects.

Besides hormone therapies, there is little on the horizon. Hormone-resistant cancer, which preferentially affects younger women, grows rapidly and has poor outcomes, can be successfully treated with chemotherapy and, in appropriate cases, Herceptin. Neither can be used for prevention, and at-risk women cannot be identified. Causation and evolution are poorly understood, so there are no effective methods to prevent it.

Other than hormones, proven risk factors for breast cancer are obesity, a sedentary lifestyle, and alcohol consumption. A common mechanism to explain these findings (insulin-related growth factor) has been proposed, but not confirmed. Lifestyle changes are the only proposed intervention.

Many theories about breast cancer causation have been disproven, including breast trauma, underarm deodorants, abortion, organochlorides, magnetic fields, and high-voltage power lines. Other drugs proposed for the prevention of breast and other cancers include the cyclo-oxygenase (COX)-2 inhibitors recently withdrawn from the market because of cardiac toxicities and dietary supplements that are in early stages of development. Vitamins do not prevent cancer, and some may increase incidence and mortality. Regular aspirin use has been associated with decreased breast cancer incidence, but has not been tested prospectively.

## Conclusion

The most promising interventions to control breast cancer lie in hormone manipulation for prevention and treatment. In the future, new drugs effective enough to cure may be found. With careful research molecular mechanisms may eventually be understood well enough to tailor treatment to each patient's individual cancer, although that goal is in the distant future. Recognizing that it took Herceptin 20 years from first proposal until its use as adjuvant therapy, patience should be expressed. Each new drug will require similarly rigorous testing, to determine which cancers may benefit and which treatment regimens will work. Despite calls from investors for rapid drug approval, shortcuts in drug development will not bring the desired results, but may endanger patients, delay or obscure important clinical findings or allow potentially useful agents to be overlooked. Translation of molecular findings into clinical practice will only work if treatment results are analyzed and compared with proven standards. Well-designed clinical trials will always be needed, and must be granted the time and money required for their performance.

*In initial adjuvant therapy for postmenopausal women with hormone receptor–positive (HR+) early breast cancer…*

# ARIMIDEX PROVEN SUPERIOR TO TAMOXIFEN IN DISEASE-FREE SURVIVAL*

## ARIMIDEX SIGNIFICANTLY IMPROVED DISEASE-FREE SURVIVAL VS TAMOXIFEN[1]

- 17% reduction in relative risk of recurrence with ARIMIDEX (424 events [n=2618]) vs tamoxifen (497 events [n=2598]) in HR+ population at a median of 68 months of follow-up ($P$<0.005)[1]
- No statistically significant difference in overall survival (intent-to-treat population) between ARIMIDEX and tamoxifen (hazard ratio=0.97; 95% CI 0.85–1.12)[1]

## WHAT YOU DO FIRST MATTERS MOST

- Risk of recurrence peaks within first 3 years postdiagnosis, and is highest in the first 5 years[2,3]

**ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor–positive early breast cancer.**

NOLVADEX® (tamoxifen citrate) is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. NOLVADEX is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. NOLVADEX reduces the occurrence of contralateral breast cancer in patients receiving adjuvant therapy with NOLVADEX for breast cancer.

### Important safety information about ARIMIDEX

ARIMIDEX is only for postmenopausal women. ARIMIDEX can cause fetal harm when administered to a pregnant woman. Before starting treatment with ARIMIDEX, pregnancy must be excluded (see **WARNINGS** section of full Prescribing Information).

Common side effects seen with ARIMIDEX vs tamoxifen in the ATAC† trial after 5 years of treatment include hot flashes (36% vs 41%), joint disorders (including arthritis, arthrosis, arthralgia) (36% vs 29%), asthenia (19% vs 18%), mood disturbances (19% vs 18%), pain (17% vs 16%), pharyngitis (14% vs 14%), nausea and vomiting (13% vs 12%), depression (13% vs 12%), hypertension (13% vs 11%), osteoporosis (11% vs 7%), peripheral edema (10% vs 11%), and headache (10% vs 8%). Fractures, including fractures of the spine, hip, and wrist, occurred more often with ARIMIDEX vs tamoxifen (10% vs 7%).

Compared to baseline, ARIMIDEX showed a mean decrease in both lumbar spine and total hip bone mineral density. Tamoxifen showed a mean increase in these measurements. Nine percent of patients receiving ARIMIDEX had an elevated serum cholesterol vs 3.5% of patients receiving tamoxifen.

Clinical and pharmacokinetic results suggest that tamoxifen should not be administered with ARIMIDEX. Estrogen-containing therapies should not be used with ARIMIDEX as they may diminish its pharmacologic action.

### Important safety information about tamoxifen

Serious and life-threatening events associated with NOLVADEX include uterine malignancies, stroke, and pulmonary emboli, some of which have been fatal. In clinical trials, uterine malignancies, including endometrial cancer and uterine sarcomas (see **WARNINGS**, Effects on the Uterus–Endometrial Cancer and Uterine Sarcoma, in full Prescribing Information), and venous thrombotic events, including pulmonary emboli, occurred 2 to 4 times more often with NOLVADEX than placebo, but each in less than 1% of women. Stroke, cataracts, and cataract surgery also occurred more often with NOLVADEX. The most frequently reported adverse reactions were hot flashes and vaginal discharge.

Women who are pregnant or plan to become pregnant should not take NOLVADEX. Women who have a history of deep vein thrombosis or pulmonary embolism or who currently use anticoagulants should not take NOLVADEX to reduce their risk of breast cancer (see **CONTRAINDICATIONS** section of full Prescribing Information).

*Please see brief summary of the full Prescribing Information on adjacent page.*

*Disease-free survival is defined as the time between randomization and the earliest occurrence of locoregional recurrence, distant recurrence, contralateral new breast cancer, or death from any cause.[1]

†ARIMIDEX, **T**amoxifen **A**lone or in **C**ombination.

**References: 1.** ARIMIDEX full Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. **2.** Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;351:1451-1467. **3.** Data on file, DA-ARI-07. AstraZeneca Pharmaceuticals LP, Wilmington, Delaware.

**www.breastcancerprofessional.com**

Arimidex®
anastrozole 1 mg tablets
*It matters to her*

## ARIMIDEX® (anastrozole) Tablets

**BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PROFESSIONAL INFORMATION BROCHURE)**

**INDICATIONS AND USAGE:** ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer. ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

**CONTRAINDICATIONS:** ARIMIDEX is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients.

**WARNINGS:** ARIMIDEX can cause fetal harm when administered to a pregnant woman. Anastrozole has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about 1 and 1.9 times the recommended human dose, respectively, on a mg/m$^2$ basis). Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about 1 and 1/3, respectively, the recommended human dose on a mg/m$^2$ basis), administered during the period of organogenesis showed that anastrozole increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses of 0.1 mg/kg/day or more. Evidence of fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), was observed in rats administered doses of 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0\text{-}24\ hr}$ that were 19 times and 9 times higher than the respective values found in postmenopausal volunteers at the recommended dose). There was no evidence of teratogenicity in rats administered doses up to 1.0 mg/kg/day. In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m$^2$ basis); there was no evidence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a mg/m$^2$ basis). There are no adequate and well-controlled studies in pregnant women using ARIMIDEX. If ARIMIDEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

**PRECAUTIONS: General:** ARIMIDEX is not recommended for use in premenopausal women as safety and efficacy has not been established (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, Effect on Estradiol** section). Before starting treatment with ARIMIDEX, pregnancy must be excluded (see **WARNINGS**). ARIMIDEX should be administered under the supervision of a qualified physician experienced in the use of anticancer agents. **Laboratory Tests:** Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving ARIMIDEX had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline. Because ARIMIDEX lowers circulating estrogen levels it may cause a reduction in bone mineral density. During the ATAC trial, more patients receiving ARIMIDEX were reported to have an elevated serum cholesterol compared to patients receiving tamoxifen (9% versus 3.5%, respectively). **Drug Interactions:** (See **CLINICAL PHARMACOLOGY**) Anastrozole inhibited *in vitro* metabolic reactions catalyzed by cytochromes P450 1A2, 2C8/9, and 3A4 but only at relatively high concentrations. Anastrozole did not inhibit P450 2A6 or the polymorphic P450 2D6 in human liver microsomes. Anastrozole did not alter the pharmacokinetics of antipyrine. Although there have been no formal interaction studies other than with antipyrine, based on these *in vivo* and *in vitro* studies, it is unlikely that co-administration of a 1 mg dose of ARIMIDEX with other drugs will result in clinically significant drug inhibition of cytochrome P450-mediated metabolism of the other drugs. An interaction study with warfarin showed no clinically significant effect of anastrozole on warfarin pharmacokinetics or anticoagulant activity. At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole (see **CLINICAL PHARMACOLOGY – Drug Interactions** and **CLINICAL PHARMACOLOGY - Clinical Studies - Adjuvant Treatment of Breast Cancer in Postmenopausal Women** subsections). Coadministration of anastrozole and tamoxifen resulted in a reduction of anastrozole plasma levels by 27% compared with those achieved with anastrozole alone. Estrogen-containing therapies should not be used with ARIMIDEX as they may diminish its pharmacologic action. **Drug/Laboratory Test Interactions:** No clinically significant changes in the results of clinical laboratory tests have been observed. **Carcinogenesis:** A conventional carcinogenesis study in rats at doses of 1.0 to 25 mg/kg/day (about 10 to 243 times the daily maximum recommended human dose on a mg/m$^2$ basis) administered by oral gavage for up to 2 years revealed an increase in the incidence of hepatocellular adenoma and carcinoma and uterine stromal polyps in females and thyroid adenoma in males at the high dose. A dose related increase was observed in the incidence of ovarian and uterine hyperplasia in females. At 25 mg/kg/day, plasma $AUC_{0\text{-}24\ hr}$ levels in rats were 110 to 125 times higher than the level exhibited in postmenopausal volunteers at the recommended dose. A separate carcinogenicity study in mice at oral doses of 5 to 50 mg/kg/day (about 24 to 243 times the daily maximum recommended human dose on a mg/m$^2$ basis) for up to 2 years produced an increase in the incidence of benign ovarian stromal, epithelial and granulosa cell tumors at all dose levels. A dose related increase in the incidence of ovarian hyperplasia was also observed in female mice. These ovarian changes are considered to be rodent-specific effects of aromatase inhibition and are of questionable significance to humans. The incidence of lymphosarcoma was increased in males and females at the high dose. At 50 mg/kg/day, plasma AUC levels in mice were 35 to 40 times higher than the level exhibited in postmenopausal volunteers at the recommended dose. **Mutagenesis:** ARIMIDEX has not been shown to be mutagenic in *in vitro* tests (Ames and E. coli bacterial tests, CHO-K1 gene mutation assay) or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats). **Impairment of Fertility:** Oral administration of anastrozole to female rats (from 2 weeks before mating to pregnancy day 7) produced significant incidence of infertility and reduced numbers of viable pregnancies at 1 mg/kg/day (about 10 times the recommended human dose on a mg/m$^2$ basis and 9 times higher than the $AUC_{0\text{-}24\ hr}$ found in postmenopausal volunteers at the recommended dose). Pre-implantation loss of ova or fetus was increased at doses equal to or greater than 0.02 mg/kg/day (about one-fifth the recommended human dose on a mg/m$^2$ basis). Recovery of fertility was observed following a 5-week non-dosing period which followed 3 weeks of dosing. It is not known whether these effects observed in female rats are indicative of impaired fertility in humans. Multiple-dose studies in rats administered anastrozole for 6 months at doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0\text{-}24\ hr}$ that were 19 and 9 times higher than the respective values found in postmenopausal volunteers at the recommended dose) resulted in hypertrophy of the ovaries and the presence of follicular cysts. In addition, hyperplastic uteri were observed in 6-month studies in female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole $C_{ssmax}$ and $AUC_{0\text{-}24\ hr}$ that were 22 times and 16 times higher than the respective values found in postmenopausal women at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in premenopausal women.

**Pregnancy: Pregnancy Category D** (See **WARNINGS**)

**Nursing Mothers:** It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIMIDEX is administered to a nursing woman (see **WARNINGS and PRECAUTIONS**).

**Pediatric Use:** The safety and efficacy of ARIMIDEX in pediatric patients have not been established.

**Geriatric Use:** In studies 0030 and 0027 about 50% of patients were 65 or older. Patients ≥ 65 years of age had moderately better tumor response and time to tumor progression than patients < 65 years of age regardless of randomized treatment. In studies 0004 and 0005 50% of patients were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients. In the ATAC study, patients who were 65 years of age or older (N=1413 for ARIMIDEX and N=1410 for tamoxifen), the hazard ratio for disease-free survival was 0.93 (95% CI: 0.80, 1.08) for ARIMIDEX compared to tamoxifen.

**ADVERSE REACTIONS**

**Adjuvant Therapy:** Adverse reaction data for adjuvant therapy are based on the adjuvant trial (see **CLINICAL PHARMACOLOGY - Clinical Studies - Adjuvant Treatment of Breast Cancer in Postmenopausal Women**). At a median follow-up of 33 months, the combination of ARIMIDEX and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for patients receiving ARIMIDEX 1 mg and tamoxifen 20 mg, respectively. Adverse events occurring with an incidence of at least 5% in either treatment group during treatment or within 14 days of the end of treatment are presented in Table 8.

**Table 8 - Adverse events occurring with an incidence of at least 5% in either treatment group during treatment, or within 14 days of the end of treatment**

| Body system and adverse event by COSTART-preferred term* | ARIMIDEX 1 mg (N=3092) | Tamoxifen 20 mg (N=3094) | Body system and adverse event by COSTART-preferred term* | ARIMIDEX 1 mg (N=3092) | Tamoxifen 20 mg (N=3094) |
|---|---|---|---|---|---|
| **Body as a whole** | | | **Musculoskeletal (continued)** | | |
| Asthenia | 575 (19) | 544 (18) | Fracture | 315 (10) | 209 (7) |
| Pain | 533 (17) | 485 (16) | Bone pain | 201 (7) | 185 (6) |
| Back pain | 321 (10) | 309 (10) | Arthrosis | 207 (7) | 156 (5) |
| Headache | 314 (10) | 249 (8) | Joint Disorder | 184 (6) | 160 (5) |
| Abdominal pain | 271 (9) | 276 (9) | Myalgia | 179 (6) | 160 (5) |
| Infection | 285 (9) | 276 (9) | **Nervous system** | | |
| Accidental injury | 311 (10) | 303 (10) | Depression | 413 (13) | 382 (12) |
| Flu syndrome | 175 (6) | 195 (6) | Insomnia | 309 (10) | 281 (9) |
| Chest pain | 200 (7) | 150 (5) | Dizziness | 236 (8) | 234 (8) |
| Neoplasm | 162 (5) | 144 (5) | Anxiety | 195 (6) | 180 (6) |
| Cyst | 138 (5) | 162 (5) | Paraesthesia | 215 (7) | 145 (5) |
| **Cardiovascular** | | | **Respiratory** | | |
| Vasodilatation | 1104 (36) | 1264 (41) | Pharyngitis | 443 (14) | 422 (14) |
| Hypertension | 402 (13) | 349 (11) | Cough increased | 261 (8) | 287 (9) |
| **Digestive** | | | Dyspnea | 234 (8) | 237 (8) |
| Nausea | 343 (11) | 335 (11) | Sinusitis | 184 (6) | 159 (5) |
| Constipation | 249 (8) | 252 (8) | Bronchitis | 167 (5) | 153 (5) |
| Diarrhea | 265 (9) | 216 (7) | **Skin and appendages** | | |
| Dyspepsia | 206 (7) | 169 (6) | Rash | 333 (11) | 387 (13) |
| Gastrointestinal disorder | 210 (7) | 158 (5) | Sweating | 145 (5) | 177 (6) |
| **Hemic and lymphatic** | | | **Special Senses** | | |
| Lymphoedema | 304 (10) | 341 (11) | Cataract Specified | 182 (6) | 213 (7) |
| Anemia | 113 (4) | 159 (5) | **Urogenital** | | |
| **Metabolic and nutritional** | | | Leukorrhea | 86 (3) | 286 (9) |
| Peripheral edema | 311 (10) | 343 (11) | Urinary tract infection | 244 (8) | 313 (10) |
| Weight gain | 285 (9) | 274 (9) | Breast pain | 251 (8) | 169 (6) |
| Hypercholesterolemia | 278 (9) | 108 (3.5) | Breast Neoplasm | 164 (5) | 139 (5) |
| **Musculoskeletal** | | | Vulvovaginitis | 194 (6) | 150 (5) |
| Arthritis | 512 (17) | 445 (14) | Vaginal Hemorrhage† | 122 (4) | 180 (6) |
| Arthralgia | 467 (15) | 344 (11) | Vaginitis | 125 (4) | 158 (5) |
| Osteoporosis | 325 (11) | 226 (7) | | | |

COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms. N=Number of patients receiving the treatment.

*A patient may have had more than 1 adverse event, including more than 1 adverse event in the same body system.

†Vaginal Hemorrhage without further diagnosis.

** The combination arm was discontinued due to lack of efficacy benefit at 33 months of follow-up.

Certain adverse events and combinations of adverse events were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs (see Table 9).

**Table 9 - Number (%) of patients with Pre-specified Adverse Event in ATAC Trial[1]**

| | ARIMIDEX, N=3092 (%) | Tamoxifen, N=3094 (%) | Odds-Ratio | 95% CI |
|---|---|---|---|---|
| Hot Flashes | 1104 (36) | 1264 (41) | 0.80 | 0.73 – 0.89 |
| Musculoskeletal Events[2] | 1100 (36) | 911 (29) | 1.32 | 1.19 – 1.47 |
| Fatigue/Asthenia | 575 (19) | 544 (18) | 1.07 | 0.94 – 1.22 |
| Mood Disturbances | 597 (19) | 554 (18) | 1.10 | 0.97 – 1.25 |
| Nausea and Vomiting | 393 (13) | 384 (12) | 1.03 | 0.88 – 1.19 |
| All Fractures | 315 (10) | 209 (7) | 1.57 | 1.30 – 1.88 |
| Fractures of Spine, Hip, or Wrist | 133 (4) | 91 (3) | 1.48 | 1.13 – 1.95 |
| Wrist/Colles' fractures | 67 (2) | 50 (2) | | |
| Spine fractures | 43 (1) | 22 (1) | | |
| Hip fractures | 28 (1) | 26 (1) | | |
| Cataracts | 182 (6) | 213 (7) | 0.85 | 0.69 – 1.04 |
| Vaginal Bleeding | 167 (5) | 317 (10) | 0.50 | 0.41 – 0.61 |
| Ischemic Cardiovascular Disease | 127 (4) | 104 (3) | 1.23 | 0.95 – 1.60 |
| Vaginal Discharge | 109 (4) | 408 (13) | 0.24 | 0.19 – 0.30 |
| Venous Thromboembolic events | 87 (3) | 140 (5) | 0.61 | 0.47 – 0.80 |
| Deep Venous Thromboembolic Events | 48 (2) | 74 (2) | 0.64 | 0.45 – 0.93 |
| Ischemic Cerebrovascular Event | 62 (2) | 88 (3) | 0.70 | 0.50 – 0.97 |
| Endometrial Cancer[3] | 4 (0.2) | 13 (0.6) | 0.31 | 0.10 – 0.94 |

[1]Patients with multiple events in the same category are counted only once in that category. [2]Refers to joint symptoms, including joint disorder, arthritis, arthrosis and arthralgia. [3]Percentages calculated based upon the numbers of patients with an intact uterus at baseline.

Patients receiving ARIMIDEX had an increase in joint disorders (including arthritis, arthrosis and arthralgia) compared with patients receiving tamoxifen. Patients receiving ARIMIDEX had an increase in the incidence of all fractures (specifically fractures of spine, hip and wrist) [315 (10%)] compared with patients receiving tamoxifen [209 (7%)]. Patients receiving ARIMIDEX had a decrease in hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events and ischemic cerebrovascular events compared with patients receiving tamoxifen. Patients receiving ARIMIDEX had an increase in hypercholesterolemia (278 [9%]) compared to patients receiving tamoxifen (108 [3.5%]). Angina pectoris was reported in 71 [2.3%] patients in the ARIMIDEX arm and 51 [1.6%] patients in the tamoxifen arm; myocardial infarction was reported in 37 [1.2%] patients in the ARIMIDEX arm and in 34 [1.1%] patients in the tamoxifen arm. Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving ARIMIDEX had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline. **First Line Therapy:** ARIMIDEX was generally well tolerated in two well-controlled clinical trials (ie, Trials 0030 and 0027). Adverse events occurring with an incidence of at least 5% in either treatment group of trials 0030 and 0027 during or within 2 weeks of the end of treatment are shown in Table 10.

**Table 10**

| Body System Adverse Event[a] | Number (%) of Subjects ARIMIDEX (N=506) | Tamoxifen (N=511) | Body System Adverse Event[a] | Number (%) of Subjects ARIMIDEX (N=506) | Tamoxifen (N=511) |
|---|---|---|---|---|---|
| **Whole body** | | | **Metabolic and Nutritional** | | |
| Asthenia | 83 (16) | 81 (16) | Peripheral Edema | 51 (10) | 41 (8) |
| Pain | 70 (14) | 73 (14) | **Musculoskeletal** | | |
| Back Pain | 60 (12) | 68 (13) | Bone Pain | 54 (11) | 52 (10) |
| Headache | 47 (9) | 40 (8) | **Nervous** | | |
| Abdominal Pain | 40 (8) | 38 (7) | Dizziness | 30 (6) | 22 (4) |
| Chest Pain | 37 (7) | 37 (7) | Insomnia | 30 (6) | 38 (7) |
| Flu Syndrome | 35 (7) | 30 (6) | Depression | 23 (5) | 32 (6) |
| Pelvic Pain | 23 (5) | 30 (6) | Hypertonia | 16 (3) | 26 (5) |
| **Cardiovascular** | | | **Respiratory** | | |
| Vasodilation | 128 (25) | 106 (21) | Cough Increased | 55 (11) | 52 (10) |
| Hypertension | 25 (5) | 36 (7) | Dyspnea | 51 (10) | 47 (9) |
| **Digestive** | | | Pharyngitis | 49 (10) | 68 (13) |
| Nausea | 94 (19) | 106 (21) | **Skin and Appendages** | | |
| Constipation | 47 (9) | 66 (13) | Rash | 38 (8) | 34 (8) |
| Diarrhea | 40 (8) | 33 (6) | **Urogenital** | | |
| Vomiting | 38 (8) | 36 (7) | Leukorrhea | 9 (2) | 31 (6) |
| Anorexia | 26 (5) | 46 (9) | | | |

[a] A patient may have had more than 1 adverse event.

Less frequent adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0030 or Trial 0027 were similar to those reported for second-line therapy. Based on results from second-line therapy and the established safety profile of tamoxifen, the incidences of 9 prespecified adverse event categories potentially causally related to one or both of the therapies because of their pharmacology were statistically analyzed. No significant differences were seen between treatment groups.

**Table 11**

| Adverse Event Group[a] | Number (N) and Percentage of Patients ARIMIDEX 1 mg (N=506) N (%) | NOLVADEX 20 mg (N=511) N (%) | Adverse Event Group[a] | Number (N) and Percentage of Patients ARIMIDEX 1 mg (N=506) N (%) | NOLVADEX 20 mg (N=511) N (%) |
|---|---|---|---|---|---|
| Depression | 23 (5) | 32 (6) | Hot Flushes | 134 (26) | 118 (23) |
| Tumor Flare | 15 (3) | 18 (4) | Vaginal Dryness | 9 (2) | 3 (1) |
| Thromboembolic Disease[a] | 18 (4) | 33 (6) | Lethargy | 6 (1) | 15 (3) |
| Venous[b] | 5 | 15 | Vaginal Bleeding | 5 (1) | 11 (2) |
| Coronary and Cerebral[c] | 13 | 19 | Weight Gain | 11 (2) | 8 (2) |
| Gastrointestinal Disturbance | 170 (34) | 196 (38) | | | |

[a] A patient may have had more than 1 adverse event. [b] Includes pulmonary embolus, thrombophlebitis, retinal vein thrombosis. [c] Includes myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia and cerebral infarct.

Despite the lack of estrogenic activity for ARIMIDEX, there was no increase in myocardial infarction or fracture when compared with tamoxifen. **Second Line Therapy:** ARIMIDEX was generally well tolerated in two well-controlled clinical trials (i.e., Trials 0004 and 0005), with less than 3.3% of the ARIMIDEX-treated patients and 4.0% of the megestrol acetate-treated patients withdrawing due to an adverse event. The principal adverse event more common with ARIMIDEX than megestrol acetate was diarrhea. Adverse events reported in greater than 5% of the patients in any of the treatment groups in these two well-controlled clinical trials, regardless of causality, are presented below:

**Table 12: Number (N) and Percentage of Patients with Adverse Event†**

| Adverse Event | ARIMIDEX 1 mg (N=262) N (%) | ARIMIDEX 10 mg (N=246) N (%) | Megestrol Acetate 160 mg (N=253) N (%) | Adverse Event | ARIMIDEX 1 mg (N=262) N (%) | ARIMIDEX 10 mg (N=246) N (%) | Megestrol Acetate 160 mg (N=253) N (%) |
|---|---|---|---|---|---|---|---|
| Asthenia | 42 (16) | 33 (13) | 47 (19) | Pharyngitis | 16 (6) | 23 (9) | 15 (6) |
| Nausea | 41 (16) | 48 (20) | 28 (11) | Dizziness | 16 (6) | 12 (5) | 15 (6) |
| Headache | 34 (13) | 44 (18) | 24 (9) | Rash | 15 (6) | 15 (6) | 19 (8) |
| Hot Flashes | 32 (12) | 29 (11) | 21 (8) | Dry Mouth | 15 (6) | 11 (4) | 13 (5) |
| Pain | 28 (11) | 38 (15) | 29 (11) | Peripheral Edema | 14 (5) | 21 (9) | 28 (11) |
| Back Pain | 28 (11) | 26 (11) | 19 (8) | Pelvic Pain | 14 (5) | 17 (7) | 13 (5) |
| Dyspnea | 24 (9) | 27 (11) | 53 (21) | Depression | 14 (5) | 6 (2) | 5 (2) |
| Vomiting | 24 (9) | 26 (11) | 16 (6) | Chest Pain | 13 (5) | 18 (7) | 13 (5) |
| Cough Increased | 22 (8) | 18 (7) | 19 (8) | Paresthesia | 12 (5) | 15 (6) | 9 (4) |
| Diarrhea | 22 (8) | 18 (7) | 7 (3) | Vaginal Hemorrhage | 6 (2) | 4 (2) | 13 (5) |
| Constipation | 18 (7) | 18 (7) | 21 (8) | Weight Gain | 4 (2) | 9 (4) | 30 (12) |
| Abdominal Pain | 18 (7) | 14 (6) | 18 (7) | Sweating | 4 (2) | 3 (1) | 16 (6) |
| Anorexia | 18 (7) | 19 (8) | 11 (4) | Increased Appetite | 0 (0) | 1 (0) | 13 (5) |
| Bone Pain | 17 (6) | 26 (12) | 19 (8) | | | | |

† A patient may have more than one adverse event.

Other less frequent (2% to 5%) adverse experiences reported in patients receiving ARIMIDEX 1 mg in either Trial 0004 or Trial 0005 are listed below. These adverse experiences are listed by body system and are in order of decreasing frequency within each body system regardless of assessed causality. **Body as a Whole:** Flu syndrome; fever; neck pain; malaise; accidental injury; infection. **Cardiovascular:** Hypertension; thrombophlebitis. **Hepatic:** Gamma GT increased; SGOT increased; SGPT increased. **Hematologic:** Anemia; leukopenia. **Metabolic and Nutritional:** Alkaline phosphatase increased; weight loss. Mean serum total cholesterol levels increased by 0.5 mmol/L among patients receiving ARIMIDEX. Increases in LDL cholesterol have been shown to contribute to these changes. **Musculoskeletal:** Myalgia; arthralgia; pathological fracture. **Nervous:** Somnolence; confusion; insomnia; anxiety; nervousness. **Respiratory:** Sinusitis; bronchitis; rhinitis. **Skin and Appendages:** Hair thinning; pruritus. **Urogenital:** Urinary tract infection; breast pain. The incidences of the following adverse event groups potentially causally related to one or both of the therapies because of their pharmacology, were statistically analyzed: weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flushes, and vaginal dryness. These six groups, and the adverse events captured in the groups, were prospectively defined. The results are shown in the table below.

**Table 13: Number (N) and Percentage of Patients**

| Adverse Event Group | ARIMIDEX 1 mg (N=262) N (%) | ARIMIDEX 10 mg (N=246) N (%) | Megestrol Acetate 160 mg (N=253) N (%) |
|---|---|---|---|
| Gastrointestinal Disturbance | 77 (29) | 81 (33) | 54 (21) |
| Hot Flushes | 33 (13) | 29 (12) | 35 (14) |
| Edema | 19 (7) | 28 (11) | 35 (14) |
| Thromboembolic Disease | 9 (3) | 4 (2) | 12 (5) |
| Vaginal Dryness | 5 (2) | 3 (1) | 2 (1) |
| Weight Gain | 4 (2) | 10 (4) | 30 (12) |

More patients treated with megestrol acetate reported weight gain as an adverse event compared to patients treated with ARIMIDEX 1 mg ($p<0.0001$). Other differences were not statistically significant. An examination of the magnitude of change in weight in all patients was also conducted. Thirty-four percent (87/253) of the patients treated with megestrol acetate experienced weight gain of 5% or more and 11% (27/253) of the patients treated with megestrol acetate experienced weight gain of 10% or more. Among patients treated with ARIMIDEX 1 mg, 13% (33/262) experienced weight gain of 5% or more and 3% (6/262) experienced weight gain of 10% or more. On average, this 5 to 10% weight gain represented between 6 and 12 pounds. No patients receiving ARIMIDEX or megestrol acetate discontinued treatment due to drug-related weight gain. Vaginal bleeding has been reported infrequently, mainly in patients during the first few weeks after changing from existing hormonal therapy to treatment with ARIMIDEX. If bleeding persists, further evaluation should be considered. During clinical trials and postmarketing experience joint pain/stiffness has been reported in association with the use of ARIMIDEX. ARIMIDEX may also be associated with rash including very rare cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome. Very rare cases of allergic reactions including angioedema, urticaria and anaphylaxis have been reported in patients receiving ARIMIDEX.

**OVERDOSAGE**

Clinical trials have been conducted with ARIMIDEX, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of ARIMIDEX that results in life-threatening symptoms has not been established. In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m$^2$ basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage). In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg/day. There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because ARIMIDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

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