

Cancer-50 Years Later

Taylor SG III, Slaughter DP, Smejkal W, Fowler EF, Preston FW. The effect of sex hormones on advanced carcinoma of the breast. *Cancer* 1948;1:604-17.

Progress in Endocrine Therapy for Breast Carcinoma

Gabriel N. Hortobagyi, M.D.

Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

Our understanding of the mechanisms of action of hormonal agents in normal and pathologic breast tissue has expanded dramatically over the last 30 years. The identification of specific receptors for estrogens, progestins, androgens, and glucocorticoids led to the elucidation of the cascade of events that results in the intended effect of steroid hormones.^{1,2} This cascade begins with the entry of the hormone into the cell, its binding to the specific receptor protein, and the signal transduction pathway that eventually results in the intended hormonal effect, such as induction of cell proliferation or division, or the production of additional hormonal receptor proteins. The contributions of multiple investigators to this process were summarized elegantly by Levenson and Jordan in 1997.³ The ability to identify and quantitate estrogen and progesterone receptor expression in individual tissues soon was followed by clinical correlations that established the diagnostic and predictive importance of these elements in the management of metastatic and primary breast carcinoma.⁴ Thus it was shown that patients with metastatic breast carcinoma whose tumors express a high concentration of estrogen receptors have a much higher probability of response to hormonal therapy than patients whose tumors express a low concentration or do not express estrogen receptors at all. Subsequent studies demonstrated that the simultaneous expression of estrogen and progesterone receptors further increased the probability of response to endocrine therapy, thus serving as a marker of an intact hormonal effector pathway.⁵ Although other clinical characteristics of the tumor such as extent of metastatic spread, patient age, duration of menopause, disease free interval, location of tumor, and, more recently, some molecular markers may influence the probability of response further, by far the degree of hormone receptor expression is the most important predictive factor.

These observations also were reproduced in the context of the primary multidisciplinary management of breast carcinoma. Thus, adjuvant hormonal therapy, mostly with the antiestrogen tamoxifen, was found to be effective in estrogen/progesterone receptor positive tumors, and essentially ineffective in those tumors without hormone receptor expression.⁶⁻¹⁰ Hormone receptor expression also was found to be an important prognostic indicator for patients with metastatic and primary breast carcinoma.¹¹ Patients with hormone receptor positive tumors have a longer survival after the development of metastasis than patients with hormone receptor negative tumors.¹²⁻¹⁶ There also is a different pattern of metastatic spread, with hormone receptor positive tumors metastasizing preferentially to soft tissues and bone, whereas hormone receptor negative tumors spread with

As *Cancer* commemorates 50 years of continuous publication, this article is one of a series of summaries on the current status of some of the oncologic issues reported in the first volume in 1948.

Address for reprints: Gabriel N. Hortobagyi, M.D., Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Box 56, 1515 Holcombe Blvd., Houston, TX 77030-4009.

Received March 16, 1998; accepted March 28, 1998.

© 1998 American Cancer Society

greater frequency to deep visceral organs, such as the liver, lung, and brain.¹⁷

In primary breast carcinoma patients with estrogen receptor negative tumors tend to have earlier recurrences and, at least during the first 5 years, a higher incidence of failure than patients with hormone receptor positive tumors. Some studies with long follow-up have suggested that after the initial 3–5 years, the prognostic value of estrogen receptor expression decreases or even disappears, with the ultimate probability of recurrence and death being similar for estrogen receptor positive and estrogen receptor negative tumors, or in some cases, even inverted.^{18–21}

While our biologic understanding of receptor activity has expanded, a quiet revolution was taking place in the development of hormonal agents. Perhaps the most influential group of these agents was the antiestrogens.²² Originally developed for purposes of contraception, tamoxifen and nafoxidine were found to have potent antiestrogenic activity.^{22,23} The initial clinical trials showed that approximately 33% of patients with previously untreated metastatic breast carcinoma, and perhaps a somewhat smaller percentage of patients with prior treatment, responded to antiestrogen therapy.²⁴ No dose response was identified, and from the very early studies it became apparent that this agent was better tolerated than all other hormonal agents available at the time. The completion of several randomized clinical trials that compared tamoxifen with estrogens,²⁵ aminoglutethimide,²⁶ progestins,^{27,28} and oophorectomy^{29,30} soon established the preeminent role of this agent as the treatment of choice for hormone-responsive metastatic breast carcinoma. Subsequent experience extended these observations to male breast carcinoma,^{31–33} and to the management of lymph node positive^{6,34,35} and lymph node negative^{6,8,36,37} breast carcinoma. Today, antiestrogens in general, and tamoxifen in particular, are considered the first-line treatment of choice for hormone-responsive metastatic breast carcinoma, and hormonal receptor positive primary breast carcinoma that requires adjuvant systemic treatment.²⁴

A second group of hormonal agents that was developed over the last 30 years includes the progestins.³⁸ Megestrol acetate^{39,40} and medroxyprogesterone acetate^{41,42} are the two principal representatives of this group. The mechanism of action of progestins is uncertain. Inhibition of gonadotrophin secretion and reduced steroid biosynthesis have been proposed; others have put forth a direct inhibition of cell growth after binding of ligand to the progesterone receptor, and down-regulation of estrogen receptor levels, resulting in reduced sensitivity of tumor cells to estro-

gen. Clinical studies have demonstrated that patients with estrogen receptor positive tumors respond better to progestins than those with estrogen receptor negative tumors. Although controversy regarding the optimal dose of progestins is ongoing, the majority of experts would agree that a dose response remains unconfirmed. Progestins are well tolerated, but cause weight gain, fluid retention, and dyspnea. For this reason, this agent usually is recommended as second-line hormone therapy after tamoxifen has outlived its usefulness.

A dramatic new development is the appearance of specific and selective aromatase inhibitors.^{43–45} Aminoglutethimide was the first aromatase inhibitor developed, but this compound was not selective, resulting in broad inhibition of adrenal steroid production. In addition, substantial toxic effects also accompanied its use in a significant minority of patients with breast carcinoma. Therefore, although its equivalence to similar endocrine interventions was established by clinical trials, the appearance of better tolerated and more selective aromatase inhibitors such as anastrozole and letrozole has completely displaced aminoglutethimide. Both anastrozole and letrozole have been shown to be more effective than progestins⁴⁶ and better tolerated than aminoglutethimide. Therefore, their therapeutic ratio appears superior to the progestins and aminoglutethimide. Currently, these agents are being compared with antiestrogens in the treatment of metastatic breast carcinoma. Furthermore, future studies will determine whether the addition of selective and potent aromatase inhibitors to other hormonal interventions, such as antiestrogens or gonadotrophin-releasing hormone analogs, will result in improved therapeutic efficacy without a substantial increase in toxic effects.

The earliest randomized trials of antiestrogens determined that these compounds were equivalent to the major surgical ablative procedures (oophorectomy, adrenalectomy, and hypophysectomy) without the irreversible effects of the surgical procedures.^{47,48} These results rapidly transformed the face of hormonal therapy, causing the total displacement of the major surgical ablations. Although ovarian ablation still is employed in some centers for reasons of cost and expediency, hormonal approaches with better therapeutic ratios are preferred.¹

The luteinizing hormone-releasing hormone (LHRH) analogs were developed to inhibit the entire hypothalamic, hypophyseal, and gonadal axis.^{1,49–51} These agents have proven to be of major efficacy in chemical gonadal ablation in both women and men. Therefore, they are used for the management of breast and prostate carcinoma with considerable success.

They are very well tolerated, with a side effect profile that compares favorably with the antiestrogens or the new aromatase inhibitors. Although the systems of administration still are evolving, these agents have numerous advantages over surgical or radiant gonadal ablation.

Although high dose estrogens seldom are used, synthetic androgens (fluoymesterone) are used in patients with persistently hormone-responsive tumors as fourth-line therapy, after antiestrogens, aromatase inhibitors, and progestins.

New Directions in Hormonal Therapy

The existing antiestrogens (tamoxifen and toremifene) have mixed estrogen agonist and antagonist effects.⁵²⁻⁵⁴ Although the antiestrogenic effect is responsible for the antitumor efficacy, the estrogen agonist effect results in maintenance of bone mineral content as well as a favorable modification of plasma lipid concentrations. However, it has been proposed that the estrogen agonist effect is responsible for the development of endometrial carcinoma,⁵⁵ and most likely for the development of antiestrogen-resistant breast carcinoma cells.⁵⁶ Recent research in antiestrogens has produced two new types of compounds. The first represent pure antiestrogens, without any agonist effects.⁵⁶ Preliminary reports suggest that these agents might be effective in tamoxifen-resistant tumors *in vitro* and *in vivo*. The long term clinical effects and the therapeutic ratio of these agents remain under investigation. The second group of agents is the selective estrogen receptor modulators (SERMs).^{57,58} These agents retain the antiestrogenic effect of tamoxifen over breast carcinoma while retaining the estrogen agonist effect over bone and plasma lipids. At the same time, they are deprived of the estrogen agonist effect over the endometrium and potentially other tissues. The Food and Drug Administration recently approved the first SERM for the management of osteoporosis. Other indications under investigation include the management of metastatic breast carcinoma, adjuvant therapy of breast carcinoma, and hormone replacement therapy in patients with a history of breast or gynecologic malignancies.

Antiandrogens, antiprogestins, and additional types of aromatase inhibitors currently are under laboratory and clinical investigation.⁵⁹

Until the late 1980s, it generally was believed that combination hormonal therapy was not more effective, but potentially more toxic than single agent hormonal manipulation. The advent of modern hormonal agents has shaken this belief. Preliminary results suggest that the addition of tamoxifen to LHRH analogs

might result in increased therapeutic efficacy.^{49,51} An additional evaluation of combined hormonal therapy, both simultaneously and in sequence, clearly is warranted.⁵⁰

There are indications that mutations in the p53 gene, the overexpression of *HER-2/neu* oncogene, and other well characterized molecular abnormalities might be associated with resistance to hormonal intervention.⁶¹⁻⁶³ If these findings are confirmed prospectively, they will lead to better selection of hormone-responsive and hormone-resistant patients for optimal therapy, and might also provide novel targets for the prevention or reversal of hormonal resistance.

The article by Taylor et al.⁶⁴ represents a classic example of enlightened empiricism. At a time when modern clinical trial methodology was unknown, and when oncology itself was just a nascent discipline, these pioneers provided an incredible lesson in the power of careful clinical observation. All their critical observations have been confirmed by subsequent studies, including the controlled randomized trials initiated several decades later. The authors reported that estrogen therapy was effective in approximately 33% of female patients. Furthermore, they observed a higher frequency of objective responses in older, postmenopausal women compared with younger women. The observation that estrogen therapy was more effective in cutaneous, subcutaneous, and lymph node metastases compared with visceral metastases also has been confirmed repeatedly. Taylor et al. also described the lack of radiographic objective responses in osseous metastases, which is more an artifact of our ability to monitor bone resorption and remodeling than a true lack of therapeutic efficacy of the hormones under study. Taylor et al. made similar observations regarding androgen therapy. However, with the use of androgens, they provided clear evidence of recalcification in bone metastases, a reproducible effect with particular relevance to androgen treatment. The authors also demonstrated response to androgens in estrogen receptor-resistant tumors, and documented the rapid relief of pain in patients with bone metastases. The phenomenon of androgen-induced tumor flare also was described in this report. The authors further observed that the duration of response to hormonal therapy was dependent on the duration of administration of hormones, and that when metastatic tumors recurred after discontinuation of hormonal treatment, reinduction was possible with the same agent. Taylor et al. reported the appearance of mixed responses. Other important observations included the fact that hormonal

therapy could down-stage inoperable locally advanced breast carcinoma patients and convert them into surgical candidates. The authors also reported a single case of male breast carcinoma with a dramatic response to hormonal therapy. Taylor et al. presented one of the earliest reports of what appears to be an objective response to testosterone in a patient with brain metastasis. Finally, the authors presented a very careful analysis of the side effects and toxicity of both estrogens and androgens in this group of patients with breast carcinoma. Their list is complete enough that more recent controlled trials have not added many new items to it.

The lesson from this article is that with commitment and dedication, careful clinical observation has an extremely important role in furthering our understanding of the behavior of a disease, as well as the therapeutic interventions under evaluation. Today, 50 years after the publication of this article, we are fortunate enough to have a much broader and deeper understanding of the natural history of breast carcinoma, as well as the mechanism of action of hormonal interventions. Furthermore, the last 50 years have given us an increasingly refined methodology for the planning and conduct of clinical trials, whereas a systematic approach to new drug development has provided us with novel, effective, and well tolerated hormonal agents. Although we stand on the shoulders of giants, we will look forward with optimism to additional developments in the management of primary and metastatic breast carcinoma.

REFERENCES

- Hortobagyi GN. Endocrine treatment of breast cancer. In: Becker KL, editor. Principles and practice of endocrinology and metabolism. Philadelphia: J.B. Lippincott Company, 1995:1868-75.
- Horwitz KB, Costlow ME, McGuire WL. MCF-7: a human breast cancer cell line with estrogen, androgen, progesterone, and glucocorticoid receptors. *Steroids* 1975;26:785-95.
- Levenson AS, Jordan VC. MCF-7: the first hormone-responsive breast cancer cell line. *Cancer Res* 1997;57:3071-8.
- McGuire WL, Carbone PP, Sears ME, Escher GC. Estrogen receptors in human breast cancer: an overview. In: McGuire WL, Carbone PP, Vollmer EP, editors. Estrogen receptors in human breast cancer. New York: Raven, 1975:1-7.
- Horwitz KB, McGuire WL. Estrogen and progesterone: their relationship in hormone-dependent breast cancer. In: McGuire WL, Raynaud JP, Baulieu EE, editors. Progesterone receptors in normal and neoplastic tissues. New York: Raven Press, 1977:103-24.
- Nolvadex Adjuvant Trial Organization. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer -Interim analysis at four years. *Lancet* 1983; i:257-61.
- The Ludwig Breast Cancer Study Group. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. *Lancet* 1984; i:1256-60.
- Anonymous. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet* 1987;2:171-5.
- Anonymous. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group [see comments]. *Lancet* 1992;339:71-85.
- Anonymous. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group [review] [see comments]. *Lancet* 1992;339:1-15.
- Knight WA, Livingston RB, Gregory EJ, McGuire WL. Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. *Cancer Res* 1977;37:4669-71.
- Howell A, Barnes DM, Harland RN, Redford J, Bramwell VH, Wilkinson MJ, et al. Steroid-hormone receptors and survival after first relapse in breast cancer. *Lancet* 1984;1:588-91.
- McGuire WL. Hormone receptors: their role in predicting prognosis and response to endocrine therapy. *Semin Oncol* 1978;5:428-33.
- Samaan NA, Buzdar AU, Aldinger KA, Schultz PN, Yang KP, Romsdahl MM, et al. Estrogen receptor: a prognostic factor in breast cancer. *Cancer* 1981;47:554-60.
- Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG. Progesterone and estrogen receptors as prognostic variables in breast cancer. *Cancer Res* 1983;43:2985-90.
- Clark GM, Osborne CK, McGuire WL. Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. *J Clin Oncol* 1984;2:1102-9.
- Clark GM, Sledge GW Jr., Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 1987;5:55-61.
- Shek LL, Godolphin W. Survival with breast cancer: the importance of estrogen receptor quantity. *Eur J Cancer Clin Oncol* 1989;25:243-50.
- Raemaekers JM, Beex LV, Koenders AJ, Pieters GF, Smals AG, Benraad TJ, et al. Disease-free interval and estrogen receptor activity in tumor tissue of patients with primary breast cancer: analysis after long-term follow-up. *Breast Cancer Res Treat* 1985;6:123-30.
- Andry G, Suci S, Pratola D, Sylvester R, Leclercq G, da Costa PM, et al. Relation between estrogen receptor concentration and clinical and histological factors: their relative prognostic importance after radical mastectomy for primary breast cancer. *Eur J Cancer Clin Oncol* 1989;25:319-29.
- Crowe JP Jr., Gordon NH, Hubay CA, Shenk RR, Zollinger RM, et al. Estrogen receptor determination and long term survival of patients with carcinoma of the breast. *Surg Gynecol Obstet* 1991;173:273-8.
- Legha SS, Carter SK. Antiestrogens in the treatment of breast cancer. *Cancer Treat Rev* 1976;3:205-16.
- Legha SS, Slavik M, Carter SK. Nafoxidine—an antiestrogen for the treatment of breast cancer. *Cancer* 1976;38:1535-41.

24. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: twenty-eight years later [review] [see comments]. *J Clin Oncol* 1995;13:513-29.
25. Matelski H, Greene R, Huberman M, Lokich J, Zipoli T. Randomized trial of estrogen vs. tamoxifen therapy for advanced breast cancer. *Am J Clin Oncol* 1985;8:128-33.
26. Lipton A, Harvey HA, Santen RJ, Boucher A, White D, Bernath A, et al. A randomized trial of aminoglutethimide versus tamoxifen in metastatic breast cancer. *Cancer* 1982;50:2265-8.
27. Ettinger DS, Allegra J, Bertino JR, Bonomi P, Browder H, Byrne P, et al. Megestrol acetate v tamoxifen in advanced breast cancer: correlation of hormone receptors and response. *Semin Oncol* 1986;13:9-14.
28. Muss HB, Wells HB, Paschold EH, Black WR, Cooper MR, Capizzi RL, et al. Megestrol acetate versus tamoxifen in advanced breast cancer: 5-year analysis—a Phase III trial of the Piedmont Oncology Association. *J Clin Oncol* 1988;6:1098-106.
29. Buchanan RB, Blamey RW, Durrant KR, Howell A, Paterson AG, Preece PE, et al. A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer. *J Clin Oncol* 1986;4:1326-30.
30. Ingle JN, Krook JE, Green SJ, Kubista TP, Everson LK, Ahmann DL, et al. Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. *J Clin Oncol* 1986;4:178-85.
31. Lopez M, Di Lauro L, Lazzaro B, Papaldo P. Hormonal treatment of disseminated male breast cancer. *Oncology (Huntingt)* 1985;42:345-9.
32. Hortobagyi GN, DiStefano A, Legha SS, Buzdar AU, Blumenschein GR. Hormonal therapy with tamoxifen in male breast cancer. *Cancer Treat Rep* 1979;63:539-41.
33. Kantarjian H, Yap HY, Hortobagyi G, Buzdar A, Blumenschein G. Hormonal therapy for metastatic male breast cancer. *Arch Intern Med* 1983;143:237-40.
34. Fisher B, Redmond C, Brown A, Wolmark N, Witliff J, Fisher ER, et al. Treatment of primary breast cancer with chemotherapy and tamoxifen. *N Engl J Med* 1981;305:1-6.
35. Anonymous. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal patients with operable breast cancer and axillary node metastasis. Ludwig Breast Cancer Study Group. *Lancet* 1984;1:1256-60.
36. Wallgren A, Baral E, Glas U, Karnstrom L, Nordenskiold B, Theve NO, et al. Adjuvant tamoxifen treatment in postmenopausal patients with operable breast cancer. *J Steroid Biochem Mol Biol* 1985;23:1161-2.
37. Love RR. Tamoxifen in axillary node-negative breast cancer: multisystem benefits and risks [review]. *Cancer Invest* 1992;10:587-93.
38. Goldhirsch A, Gelber RD. Endocrine therapies of breast cancer [review]. *Semin Oncol* 1996;23:494-505.
39. Muss HB, Cruz JM. High-dose progestin therapy for metastatic breast cancer [review]. *Ann Oncol* 1992;3(Suppl 3):15-20.
40. Canetta R, Florentine S, Hunter H, Lenaz L. Megestrol acetate. *Cancer Treat Rev* 1983;10:141-57.
41. Muss HB, Case LD, Atkins JN, Bearden J, 3rd, Cooper MR, Cruz JM, et al. Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study [see comments]. *J Clin Oncol* 1994;12:1630-8.
42. Cavalli F, Goldhirsch A, Jungi F, Martz G, Mermillod B, Alberto P. Randomized trial of low- versus high-dose medroxyprogesterone acetate in the induction treatment of postmenopausal patients with advanced breast cancer. *J Clin Oncol* 1984;2:414-9.
43. Anonymous. New aromatase inhibitors for breast cancer [review]. *Drug Ther Bull* 1997;35:55-6.
44. Brodie AM, Njar VC. Aromatase inhibitors and breast cancer [review]. *Semin Oncol* 1996;23:10-20.
45. Buzdar AU, Plourde PV, Hortobagyi GN. Aromatase inhibitors in metastatic breast cancer. *Semin Oncol* 1996;23:28-32.
46. Buzdar AU, Jones SE, Vogel CL, Wolter J, Plourde P, Webster A. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. *Cancer* 1997;79:730-9.
47. Nemoto T, Patel J, Rosner D, Dao TL. Tamoxifen (Nolvadex) versus adrenalectomy in metastatic breast cancer. *Cancer* 1984;53:1333-5.
48. Wells SA Jr., Santen RJ. Ablative procedures in patients with metastatic breast carcinoma. *Cancer* 1984;53:762-5.
49. Klijn JGM, Seynaeve C, Beex L, Mauriac L, van Zijl J, Veyret C, et al. Combined treatment With busserelin (LHRH-A) and tamoxifen vs single treatment with each drug alone in premenopausal metastatic breast cancer: preliminary results of EORTC study 10881 [abstract 132]. *Proc Am Soc Clin Oncol* 1996;15:117.
50. Taylor CW, Green S, Dalton WS, Martino S, Ingle JN, Robert NJ, et al. A multi-center randomized trial of zoladex versus surgical ovariectomy in pre-menopausal patients with receptor positive metastatic breast cancer [abstract 19]. *Breast Cancer Res Treat* 1996;37:37.
51. Boccardo F, Rubagotti A, Perrotta A, Amoroso D, Balestrero M, de Matteis A, et al. Ovarian ablation versus goserelin with or without tamoxifen in pre-perimenopausal patients with advanced breast cancer: results of a multicentric Italian study. *Ann Oncol* 1994;5:337-42.
52. Jordan VC. Estrogen receptor-mediated direct and indirect antitumor effects of tamoxifen. *J Natl Cancer Inst* 1990;82:1662-3.
53. Love RR, Newcomb PA, Wiebe DA, Surawicz TA, Jordan VC, Carbone PP, et al. Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer [see comments]. *J Natl Cancer Inst* 1990;82:1327-32.
54. Jordan VC. Molecular mechanisms of antiestrogen action in breast cancer [review]. *Breast Cancer Res Treat* 1994;31:41-52.
55. Assikis VJ, Jordan VC. Tamoxifen and endometrial cancer: from experiment to patient [review]. *Recent Results Cancer Res* 1996;140:61-71.
56. Catherino WH, Jordan VC. A point mutation in the estrogen receptor from a tamoxifen-stimulated human breast cancer can explain the change of tamoxifen pharmacology from an antiestrogen to an estrogen [abstract]. *Breast Cancer Res Treat* 1994;32:32.
57. Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Arnaud C. A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. *J Bone Miner Res* 1996;11:835-42.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.