Case Study Findings Report

The MA 17 Clinical Trial:
A Paradigm Shift for Breast Cancer Adjuvant Therapy

Presented to:

The Canadian Cancer Society Research Institute

Presented by:

Steve Montague, Performance Management Network Inc.
Rudy Valentim, Canadian Cancer Society Research Institute

Date:

August, 2010
# Table of Contents

Executive Summary ........................................................................................................... i  
1.0 Introduction .................................................................................................................. 1  
2.0 Background ................................................................................................................... 1  
3.0 Roles and Relationships .............................................................................................. 4  
4.0 MA 17 Clinical Trial ...................................................................................................... 5  
5.0 MA 17 Clinical Trial Performance Story ....................................................................... 8  
6.0 Estimating Impacts of the MA 17 Clinical Trial ........................................................... 14  
7.0 Incrementality ............................................................................................................... 17  
8.0 Barriers Overcome by the MA 17 Clinical Trial ........................................................... 18  
9.0 Observations and Recommendations ......................................................................... 19  
Appendix A: Estimating the Impacts of Health Research ................................................... 23  
Appendix B: Methodology, Limitations & Lessons Learned .............................................. 30  
Appendix C: Literature Review .......................................................................................... 34
Acknowledgements

The study team would like to particularly thank Dr Shepherd, Dr Pritchard, Dr Goss, Dr Ingle, Dr Grunfeld, Dr Pater, Mr. Jeff Martens and the team at Novartis, the leadership of the Clinical Trials Group as well as key professional staff of the Canadian Cancer Society for their help in assembling this case study. Having recognized these contributions, all errors or omissions are the responsibility of the authors.
Executive Summary

Up until the early 2000s, the standard for adjuvant treatment of post-menopausal women with early stage, hormone receptor-positive (HR+) breast cancer was the prescription of a drug named tamoxifen. A selective estrogen receptor modulator, tamoxifen works by binding to the estrogen receptor thus keeping cells from making or using estrogen. While tamoxifen was shown to be effective at reducing cancer recurrence risk for the first few years after surgery, research demonstrated that continuing tamoxifen therapy for longer than five years did not improve recurrence-free or overall survival and could actually be harmful (Burstein, 2003). There were no widely accepted treatments available beyond five years, yet research showed that a significant risk of recurrence for breast cancer still remained. Oncologist and cancer researcher Dr Paul Goss, currently of the Massachusetts General Hospital Cancer Center, had preliminary research findings which suggested that the administration of an aromatase inhibitor, a class of drugs that, unlike tamoxifen, actually suppress the synthesis of estrogen, could be an effective adjuvant therapy for postmenopausal women with HR+ breast cancer. He approached the Canadian Cancer Society (the Society) funded NCIC Clinical Trials Group (CTG), a cooperative oncology network based at Queen’s University, with the idea for a clinical trial using an aromatase inhibitor sequentially with tamoxifen to reduce breast cancer recurrence in post menopausal women with HR+ breast cancer. Dr Goss eventually led a group that would test this hypothesis by conducting the MA 17 clinical trial. The MA 17 clinical trial was activated in August 24, 1998 and met patient accrual by mid-2002. The trial was organized and coordinated across two continents, six distinct institutional groups, nine countries and 416 sites by the CTG. An interim analysis of the planned five year study demonstrated results that were so convincing that CTG leadership, in consultation with the data and safety monitoring committee (DSMC), decided to terminate the trial early and unblind the study in October, 2003 in order to disseminate the remarkable preliminary results. In November 2003, CTG published the findings in the New England Journal of Medicine, showing that the use of the aromatase inhibitor letrozole significantly reduced the risk of breast cancer recurrence in the extended adjuvant setting. This led to a virtually immediate and traceable change in treatment practices.

The MA 17 trial advanced the availability of an effective therapy in a clinical setting where there had not been one before. Under the strong leadership of principal investigator Dr Goss, and with the engaged support of a diverse set of researchers, the CTG delivered persuasive evidence that has had a global impact on preventing disease recurrence in women surviving HR+ breast cancer. This reach was facilitated by the ability of the CTG to attract of a strong group of prestigious international researchers and institutions to the trial. Upon study unblinding, there was a widely distributed press release, followed by a number of highly-cited publications. Post trial market research conducted by the pharmaceutical company that participated in the trial suggested that prescribing physicians recalled the name of the trial (MA 17), the name of the principal investigator (Dr Goss) and the coordinating centre of the trial (CTG) in an essentially unprecedented fashion, suggesting that the trial directly influenced their prescribing patterns.

Critical factors in advancing this very successful clinical trial were the broad network structure of the CTG, including loose ties to several key groups and a potentially low perceived bias towards any given group or approach, the longstanding quality of work and reputation of the CTG Breast Disease Site Committee (Breast DSC) and the drive of the principal investigator Dr Goss. Also worth noting is the Society’s long history of funding hormone base breast cancer research, which although not established as fundamental to the trial itself was part of the foundational endocrine-related breast cancer research that preceded and undoubtedly informed the trial. This point highlights the value of funding discovery-based cancer research.
as it contributes to the knowledge base and research capacity that may ultimately inform and lead to important breakthroughs further down the research and development (R&D) and innovation spectrum.

The MA 17 trial had a profound impact on a number of different areas, both directly in the form of follow-on related clinical trials, and indirectly by encouraging an increased research focus on late to extended adjuvant breast cancer therapy and increasing the use of aromatase inhibitors in all (early, late and extended) adjuvant settings. The results of the MA 17 trial have contributed to changing world-wide standard of care practices and are cited prominently in provincial, national and international guidelines for the adjuvant treatment of breast cancer. Most importantly, the MA 17 clinical trial was responsible for hundreds and possibly thousands of disease free years for Canadian women. It has almost certainly created thousands of disease free years worldwide.

The prospective implications of this successful clinical trial are many. The scientific implications continue today, and go beyond the scope of this case study. From a management perspective, the value of the MA 17 trial is that it demonstrated wide and heterogeneous reach. The CTG offered a clinical trial infrastructure which provided investigators access to international expertise, wide regional and international trial sites and ‘independent’ guidance. The guidance and leadership CTG demonstrated was critical, as it allowed for the coordination of several groups with different primary interests to work towards the same common goal. This was facilitated by the credibility of the CTG investigators and the perception that it was not tied too closely to any specific scientific interests. As such, this case study shows that there is an important place in the cancer research and clinical trial environments for a high quality, widely connected and independent group such as the CTG. Furthermore, when such a group is driven by a clear mission it will overcome institutional biases and barriers to achieve its goals.

Key Conclusions:

- The Society’s long history of funding endocrine-related breast cancer research contributed to the scientific knowledge base and research capacity that informed the trial, which points to the value of funding discovery based basic and translational cancer research.

- The MA 17 clinical trial led to immediate and traceable changes in world-wide standard of care practices and is responsible for hundreds and certainly thousands of disease free years in women worldwide.

- The coordination of the MA 17 clinical trial was facilitated by the credibility of the CTG and its Breast Disease Site Committee, its ability to attract high impact investigators like Dr Goss, and its capacity to act as an independent broker among the various interests and potential biases surrounding cancer treatment at the time.

- The CTG is a valuable asset for the Society, as it has built an international reputation, networks clinical trial centres and oncologists across the country, provides researchers with access to wide regional trial opportunities and clinical samples, and has world class management expertise.
1.0 Introduction

This case study focuses on the MA 17 clinical trial conducted by the CTG which receives foundational funding from the Society. The MA 17 trial was the first reported large extended adjuvant trial looking at the efficacy of using an aromatase inhibitor (letrozole) following the use of tamoxifen for post-menopausal women being treated for HR+ breast cancer.

The purpose of this case study is to document the immediate and long-term impacts of this seminal trial and demonstrate pathways from research to knowledge translation and impact. This is accomplished by focussing on the entire research science spectrum from basic science through to clinical practice change and using the Society’s results chain hierarchy as an organizing structure to describe the inputs, activities and sequence of impacts which occurred before, during and after the MA 17 trial. A secondary objective is to provide a learning aspect for the Society regarding the mission effectiveness of providing infrastructure funding for this type of large scale research initiative.

Case study methodology included a document review, key stakeholder interviews, and a literature review.

More details on the methodology and its limitations are contained in Appendix B.

2.0 Background

Breast cancer remains one of the biggest cancer threats to Canadians. Over 22,000 Canadian women are diagnosed with breast cancer every year and one in nine Canadian women can expect to develop breast cancer in their lifetime (Canadian Cancer Society, 2010). It is the most common cancer among Canadian women.

As far back as the late 1800s, there were case reports of oophorectomy (removal of ovaries) benefiting patients with breast cancer (Beatson, 1896) and the subsequent application of oophorectomy and adrenalectomy in the 1950s for patients with advanced breast cancer set the foundation for the critical role that hormonal manipulation currently plays in the treatment of breast cancer (Huggins & Dao, 1953). In Canada, like most developed countries, approximately 70% of breast cancers express the estrogen receptor (Joslyn, 2002) and hormonal manipulation to block or inactivate the receptor or reduce the amount of estrogen available has been an important advance in the treatment of breast cancer (Early Breast Cancer Trialists’ Collaborative Group, 2005).

In the adjuvant setting (directly after surgery to prevent recurrence), anti-estrogen therapy has been shown to reduce the risk of breast cancer recurrence and death amongst post-menopausal women with early stage, HR+ breast cancer. Up until the early 2000s, the standard for adjuvant hormonal treatment of early stage, HR+ breast cancer had been tamoxifen citrate (tamoxifen), a selective estrogen receptor modulator (SERM) (Early Breast Cancer Trialists’ Collaborative Group, 2005). As a SERM, tamoxifen exerts both antagonistic and agonistic effects on the estrogen receptor, depending on the tissue, the hormonal milieu and likely depending on what other receptor pathways and coregulators are activated. Tamoxifen has been well studied and reduces the risk of death from breast cancer by approximately 22%, and the risk of recurrence by 42% (Early Breast Cancer Trialists’ Collaborative Group, 2005).

Research also suggested that the optimal time course for adjuvant tamoxifen usage was 5 years\(^1\), which had become the standard practice. Continuing tamoxifen therapy for longer than 5 years did not improve recurrence-free or overall survival and could actually be harmful. As such,

\(^{1}\) A review of the literature and key stakeholder interviews confirmed this point.
despite the clinical success of tamoxifen attempts were made to find alternate pharmacologic strategies that were more effective in the adjuvant setting.

Aromatase Inhibitors
Aromatase inhibitors prevent the formation of the female hormone estradiol (an estrogen) by interfering with an aromatase enzyme, which synthesizes estrogen. They are used primarily as a type of hormone therapy for postmenopausal women who have hormone-dependent breast cancer (National Cancer Institute, n.d.). Aromatase inhibitors are not used in the treatment of premenopausal women with breast cancer because most of the estrogen is produced by the ovaries and not by the conversion of androgens to estrogen. Aromatase inhibitors can be categorized into two distinct categories: steroidal/irreversible and nonsteroidal/reversible inhibitors of estrogen synthesis (Lake & Hudis, 2002). Currently, three aromatase inhibitors are available: anastrozole, letrozole, and exemestane. A variety of side effects are associated with the use of aromatase inhibitors including: an increase in joint disorders, increase in incidence of osteoporosis and fractures, and hypercholesterolemia.

Early Development of Aromatase Inhibitors
The development of aromatase inhibitors can be traced back to the 1920s with the initial discovery of estrogens and their bioactivity in urinary extracts (Santen, Brodie, Simpson, Siiteri, & Brodie, 2009). This discovery provided the drive to better understand estrogens. The need to better understand estrogen in the context of breast cancer is important because estrogen itself can promote the growth of breast cancer cells. Some breast cancers are classified as estrogen receptor-positive, which means that they have a protein to which estrogen will bind. These breast cancer cells need estrogen to grow (National Cancer Institute, n.d.). In the 1930s, work began on the isolation and biochemical characterization of androgens and estrogens. This work led to the recognition of similarities between these two compounds and the fact that the male androgen hormone could be converted to the female estrogen hormone (Santen et al., 2009). The research focus migrated to estrogen synthesis and metabolism in the 1940s as a result of the focus on developing oral contraceptives during that period (Santen et al., 2009). Throughout the 1950s and 1960s, work continued on estrogen biosynthesis. An immense amount of research was conducted during this period which resulted in better understanding of the “aromatization process”; that is, the process by which the enzyme aromatase converts androgens into estrogens. The development of an aromatase assay requiring only one step was a critical advancement of the time, which facilitated the study of potential aromatase inhibitors in later experiments (Santen et al., 2009). By the 1970s a consensus around the aromatization process began to develop amongst investigators. As a result, the therapeutic potential of targeting aromatase came into focus and work on the development of selective aromatase inhibitors began (Santen et al., 2009). It was also during this time that the idea of using aromatase inhibitors in treating breast cancer patients was cemented. A key discovery during this period was the extraglandular aromatase activity in both men and women. Up to this point it was believed that steroid hormones were only produced in glands such as ovary, testis, and adrenal (Santen et al., 2009). Investigators also began to show that body fat was a rich source of aromatase and breast tissue in particular was found to have significant aromatase activity.

Steroidal Aromatase Inhibitors
As further discoveries about the aromatization process were being made, investigators began working on identifying steroidal aromatase inhibitors. Eventually, after extensive comparisons amongst inhibitors, a lead compound (4-OH-A) was identified. In the mid-1980s clinical trials with 4-OH-A for treatment of breast cancer in women were conducted and 4-OH-A (renamed formestane) became the first steroidal aromatase inhibitor to become available for the treatment of breast cancer (Santen et al., 2009).

2 It is the comparable estimation of the nature, constitution or potency of the active principles with that of the standard drug, by means of the reaction on a living matter such as whole animal, isolated tissue or organism.
**Non-Steroidal Aromatase Inhibitors**
At the same time, work on developing non-steroidal aromatase inhibitors was also taking place. In the 1950s and 1960s endocrinologists began focusing on the development of alternatives to surgery and subsequently hormone additive therapy emerged (Santen et al., 2009). The most widely accepted approach included using aminoglutethimide (AG) in combination with hydrocortisone (HC) to inhibit adrenal steroid synthesis (Santen et al., 2009). A practical AG/HC regimen was established and pilot studies were conducted. After numerous studies, in the mid-1970s it was proven that AG inhibited aromatase in postmenopausal patients with breast cancer, which led to its designation as a non-steroidal first generation aromatase inhibitor (Santen et al., 2009). The next step involved comparing the AG/HC regimen to surgical adrenalectomy and hypophysectomy. AG/HC was demonstrated to be as effective as adrenalectomy and hypophysectomy, both in clinical responses and estrogen suppression and led to the abandonment of the surgical ablative methods (Santen et al., 2009). Another important comparison to take place was between AG/HC and tamoxifen (an antiestrogen compound). Tamoxifen was being developed at approximately the same time as AG in the 1970s (Santen et al., 2009). Four randomized clinical trials compared the two approaches and found them to be equally effective, but tamoxifen showed fewer side effects and toxicity than AG (Santen et al., 2009). Also, the fact that AG relied on the coadministration of HC cemented tamoxifen as the first line hormonal therapy for breast cancer, a position still held today (Lake & Hudis, 2002).

**Current Day “Third-Generation” Aromatase Inhibitors**
In the 1980s, an important international conference took place in Florida, bringing together researchers to discuss a broad range of basic and clinical aspects of aromatase. It proved the catalyst for investment of resources into the development of future aromatase inhibitors and the optimization of aromatase inhibitor therapy (Santen et al., 2009). As the potential of aromatase inhibitors increased, pharmaceutical companies began investing in the development of both steroidal and nonsteroidal aromatase inhibitors. Ciba-Geigy (now Novartis), Merrill-Dow, Imperial Chemical Industries (now AstraZeneca), Lilly, Pharmitalia, Jannsen, and Yamaguchi pharmaceuticals all launched aromatase inhibitor development programs (Santen et al., 2009). The most notable of the second generation aromatase inhibitors to be released during this time was fadrozole. Questions about its efficacy, however, never allowed it to achieve substantial usage. The need for more potent aromatase inhibitors continued and pharmaceutical companies began using more sophisticated approaches including structure/function analysis, animal models, and hormone assays to identify lead compounds (Santen et al., 2009). Ultimately, this work led to the development of current day third generation aromatase inhibitors. Two nonsteroidal reversal inhibitors, letrozole (produced by Novartis) and anastrozole (produced by AstraZeneca), and one mechanism based steroidal inhibitor, exemestane (produced by Pfizer). These third-generation aromatase inhibitors possess 100 to 10,000 fold higher potency and greater efficacy and less toxicity than their precursors (Santen et al., 2009). A variety of clinical trials were subsequently conducted to demonstrate the superiority of aromatase inhibitors over tamoxifen and the AG/HC regimen. All trials showed to varying degrees the superiority of aromatase inhibitors with respect to clinical efficacy. These trials led to the global approval of all three third-generation aromatase inhibitors as first-line therapy for advanced breast cancer and then later in the adjuvant setting. Several other studies (including the MA 17 trial) compared the sequential use of aromatase inhibitors after the initial adjuvant therapy with tamoxifen. As a result, it is now recommended to use an aromatase inhibitor in the course of adjuvant therapy (Santen et al., 2009).

**Letrozole**
Letrozole was the aromatase inhibitor used in the MA 17 clinical trial. It is a third generation aromatase inhibitor developed by the pharmaceutical company Novartis. Its origins date back to 1986 when a set of compounds were tested by Novartis using a newly developed assay. While testing they discovered that one compound, later named letrozole, was infinitely more potent than any other aromatase inhibitor compounds previously tested by Novartis (Bhatnagar, 2007). Following this preclinical discovery a variety of clinical trials were organized to further test and optimize the efficacy of letrozole. This ultimately culminated in the drug being approved for the
treatment of advanced breast cancer (second-line metastatic) in 1997 (Bhatnagar, 2007). After further testing and trials, letrozole was approved for use as a first-line treatment (first-line metastatic) in 2001; as an extended adjuvant (following the use of tamoxifen) in 2004 (a direct result of the CTG MA 17 clinical trial); and finally, as an initial adjuvant (following surgery) in 2005 (Novartis, 2010).

**Canadian Cancer Society Funding of Hormone Based Breast Cancer Research**

The Society has had a long history of funding research in the area of hormone based breast cancer research having provided countless research grants to investigators working in this broad research area. For instance, a keyword search of Canadian Cancer Society Research Institute (CCSRI) funding database shows that the Society invested in 19 research grants in this area totalling over $1.9 million from 1947 to 1997, a year prior to the trial being activated. Since then, the Society has funded a further 39 grants totalling over $15.8 million. The Society has funded the work of a variety of key breast cancer researchers in this area including: Dr Norman Boyd, Dr Paul Goss, Dr Kathleen Pritchard, Dr Trevor Archer, Dr Geoffrey Hammond, Dr Vincent Giguere, and Dr Donald Killinger. Most notably, Dr Goss was the principal investigator of the MA 17 clinical trial and Dr Pritchard led the CTG Breast Disease Site Committee (Breast DSC) during the time in which the trial took place. Arguably, the Society’s long history of funding endocrine-related breast cancer research contributed to the scientific knowledge base and research capacity that informed the trial.

### Roles and Relationships

**The NCIC Clinical Trials Group**

The CTG is an academic cooperative group that receives core funding from the Society through a peer-reviewed grant administered by the CCSRI. The CTG is the only adult cancer clinical trials cooperative group based in Canada that has a national membership and is committed to assessing all types of therapy across the spectrum of different cancer types. The CTG’s mission is to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease. The CTG includes more than 80 Canadian member institutions, all major cancer centers and many community hospitals, and more than 1200 investigator, research nurse, data manager and pharmacist members. Between its inception in 1980 and 2010, the CTG has conducted or is conducting 430 phase I, II or III clinical trials. The CTG conducts trials in all major cancer types and tests strategies that include systemic therapy (e.g., chemotherapy, biologic therapy), radiation therapy, surgery, dietary supplementation and strategies associated with lifestyle change.

Current core funding provided by the Society is just over $5 million per year, which comprises about 20% of the CTG’s total funding. CTG states that this 20% is the critical base or core upon which all the other funding is made possible. Funds provided by the Society are essential to the CTG’s infrastructure and its abilities to leverage and independently conduct trials that would not otherwise be possible. The sources of the other 80% of funding include peer-review grants, US National Cancer Institute’s Cancer Therapy Evaluation Program (CTEP), and industry support of selected clinical trials.

**The CTG Breast Disease Site Committee**

The CTG is structured in a way that is typical for a clinical trials cooperative group. The CTG is comprised of fifteen committees including eleven disease site committees, which represent the major disease sites of cancer such as the breast, lung, etc. These committees are responsible for developing a disease-specific strategy and specific trials that advance that strategy. The Breast

---

3 Keywords included aromatase inhibitors, letrozole, tamoxifen, herceptin, adjuvant therapies, estrogen synthesis, estrogen inhibitors, estrogen metabolism, estrogen receptor, anastrozole, roloxifene, exemestane.

4 Grants include Canadian Breast Cancer Research Alliance (CBCRA) research grants. CBCRA is a multi-partnered initiative, of which the Society was a founding partner providing $2.5 million per year in funding.
DSC was responsible for the MA 17 trial and is comprised of a group of CTG investigators from across Canada spanning all disciplines.

The group functions through collaboration and consensus, encouraging and receiving proposals from members across the country. The group also develops all trial concepts through their Executive, conducting surveys of members to assess interest and feasibility. Proposals are ranked and presented for consideration to the Clinical Trial Committee of the CTG.

The CTG Breast DSC has a long history of active participation and involvement with many clinical trials groups, both in the national and international arena. Most notably, the CTG Breast DSC has been involved with the North American Breast Cancer Groups (NABCG), the Breast International Group (BIG), the International Breast Cancer Study Groups (IBCSG), and the European Organization for Research and Treatment of Cancer (EORTC).

The Canadian Cancer Society
The CTG has its origins and receives core funding from the Society via a CCSRI (previously NCIC) research grant. The funding provided by the CCSRI grant provides support to faculty and staff within the CTG central office, some per-case funding to member institutions for accrual, and a subset of operational costs. Funding from the CCSRI grant represents 20 percent of the CTGs’ total funding, yet as described in more detail above, this 20% is the critical core funding upon which all the other funding is made possible.

4.0 MA 17 Clinical Trial

The MA 17 clinical trial proposed to conduct a randomized study comparing the use of an aromatase inhibitor with a placebo in postmenopausal women with HR+ early-stage breast cancer after five years of adjuvant tamoxifen treatment. The CTG was to lead and operate the study in collaboration with the manufacturer of an aromatase inhibitor and major North American and European (breast) cancer research groups. The original industry partner was to be Johnson & Johnson Pharmaceutical Research and Development as they had agreed to supply their aromatase inhibitor vorozole for the purposes of the MA 17 trial. It was selected for the trial because Dr Goss had intimate knowledge of the drug and it had previously shown clinical value. Protocols were established and international partnerships in place, but at the last moment Johnson & Johnson Pharmaceutical Research and Development pulled out of the trial, which necessitated a replacement. Through previous work and links to a diverse set of networks Dr Goss and the CTG were aware of another aromatase inhibitor, named letrozole, produced by the pharmaceutical company Novartis. They approached the manufacturer with the opportunity to join the trial, which it did after some deliberation. Dr Goss and the CTG spent almost a full year convincing Novartis to join the trial, which delayed its activation.

In the end, the industry partner Novartis contributed approximately $13 million to the trial which covered the costs associated with the drug letrozole, the placebo and patient recruitment. The study also included the involvement of the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), Cancer and Leukemia Group B (CALGB), North Central Cancer Treatment Group (NCCTG), European Organization for Research and Treatment of Cancer (EORTC), and the International Breast Cancer Study Group (IBCSG). Institutional review boards of participating health care institutions approved the study protocol, and all patients (5,187 women) gave written informed consent. Trial sites numbered 416 and the trial took place across 9 countries in North America and Europe (Canada, United States, England, Belgium, Ireland, Italy, Poland, Portugal and Switzerland).

The trial was activated on August 24, 1998 and was designed to determine whether prolonged adjuvant hormonal therapy using letrozole after five years of initial therapy with tamoxifen was

---

5 Reasons for the pull out were never fully disclosed and/or recalled by key stakeholders during interviews.
superior to tamoxifen therapy alone. It was a phase III, randomized, double-blind placebo-controlled trial comparing letrozole with placebo in postmenopausal women with HR+ early-stage breast cancer. Patients were randomly assigned to receive either letrozole (2.5 mg) or placebo daily for 5 years. The unusual use of a placebo comparison group was approved because there was no alternative therapy prescribed by international bodies at the time beyond the standard initial five years of tamoxifen. The primary endpoint of the trial was disease-free survival and secondary endpoints were quality of life, overall survival, and long-term safety. The trial design is summarized in Figure 1 (NCIC Clinical Trials Group, 2009).

Figure 1. MA 17 randomized trial design.

The trial had a projected patient accrual of 4800 patients, which was met by mid-2002 and subsequently exceeded. Overall, 5,187 women participated in the trial and were randomized to take either letrozole \((n = 2,593)\) or placebo \((n = 2,594)\). As a result of reported noncompliance, 10 patients in the letrozole group and seven in the placebo arm were initially excluded from all analyses, leaving 5,170 patients (2,583 on letrozole and 2,587 on placebo). The final safety analysis excluded a further 21 patients who never received study medication, yielding a final safety population of 5,149 patients, 2,572 received letrozole and 2,577 received placebo.
The first planned interim analysis took place in March of 2003 and the results indicated significant improvement in the outcomes of patients taking letrozole. There were 132 breast cancer recurrences in the placebo group and 75 recurrences in the letrozole group. Based on this 43% reduction in recurrence risk ($P = 0.00008$) with letrozole seen in the interim analysis at 2.4 years’ median follow-up, the CTG DSMC recommended that the MA 17 trial be terminated and the participants promptly informed of the results. In October 2003, the trial was unblinded and patients on placebo were given the opportunity to switch to letrozole. Updated efficacy results after a median follow-up of 30 months confirmed the significant clinical benefits of letrozole in the extended adjuvant therapy setting (Goss et al., 2007).

The fundamental findings of the MA 17 trial as described by Dr Goss (2007) were as follows:

At 30 months’ follow-up, letrozole significantly improved disease-free survival (DFS), the primary end point, compared with placebo (Figure 2). The four year DFS for patients receiving letrozole was 94.4%, compared with 89.8% for patients receiving placebo. The hazard ratio for recurrence or contralateral breast cancer was 0.58 (95% confidence interval [CI] 0.45, 0.76; $P \leq 0.76$), representing a 42% reduction in risk for letrozole relative to placebo. The updated analysis also showed that letrozole produced a statistically significant improvement in distant disease-free survival (DDFS) (hazard ratio $= 0.60; 95\% \text{ CI} \ 0.43, 0.84; P = 0.002$), which may be regarded as a more meaningful end point than overall DFS; women with distant metastases inevitably die of breast cancer, and an improvement in DDFS may therefore translate into longer overall survival. Letrozole treatment non-significantly prolonged time to contralateral breast cancer incidence, resulting in a 37.5% relative risk reduction compared with placebo.

![Figure 2. Kaplan–Meier curves for disease-free survival in the updated analysis of MA 17. N, number at risk; S, survival percent, with 95% confidence intervals (CIs) in parentheses.](image)

The prospectively planned subgroup analysis showed that letrozole significantly improved DFS in all patients, irrespective of nodal status. The reduction in risk of recurrence in node-positive tumors was 39% (hazard ratio $= 0.61; 95\% \text{ CI} \ 0.45, 0.84$), and 55% in those with node-negative tumors (hazard ratio $= 0.45; 95\% \text{ CI} \ 0.27, 0.73$). While overall survival (OS) was not significantly improved (hazard ratio $= 0.82; 95\% \text{ CI} \ 0.57, 1.19; P = 0.3$), letrozole significantly improved OS in patients with node-positive tumors (hazard ratio $= 0.61; 95\% \text{ CI} \ 0.38, 0.98; P = 0.04$) and this was the first survival advantage demonstrated by an aromatase inhibitor in early breast cancer.
At the time of the study unblinding, a press release was jointly announced by the Society and NCIC, the US National Cancer Institute (US NCI) and the Princess Margaret Hospital, the institution with which Dr Goss was affiliated during the trial. According to interviewees, the worldwide media coverage was unprecedented for this kind of announcement. The decision to unblind the study after less than half the designed trial time was a very rare occurrence and resulted in much discussion amongst the international research community. Notably, the study of overall survival and other sub-studies essentially continued after the trial was unblinded. MA 17B investigated the influence of letrozole on bone mineral density and MA 17L investigated the influence of letrozole on serum lipid concentrations.

The results of the MA 17 trial were published (Goss et al., 2003) in the New England Journal of Medicine in November, 2003. In all, 19 research papers have resulted from this trial and have been published in high impact journals like the New England Journal of Medicine and the Journal of Clinical Oncology. According to the Web of Science, the primary publication has been cited a total 721 times as of April, 2010. In addition, a total of 28 abstracts have been presented or published based on the results of the MA 17 trial.

Further outcomes and observed impacts are described in subsequent sections.

5.0 MA 17 Clinical Trial Performance Story

The conceptual framework of this case study is based on the Society’s results chain hierarchy. This marks the Society’s first attempt at using its structured hierarchy of results to describe the performance story in a case study. Its approach is focused on an agreed hierarchy of results with mission ends at the top. As such, the case is intended to demonstrate a direct connection to the eradication of cancer. Additionally, the approach used in this case study attempts to build in an appreciation (to the extent possible) of the multi-year build-up of research and innovation support which led to the MA 17 trial, recognizing the trial as part of a science and innovation pathway of connections.

Results Chain Hierarchy

The results chain hierarchy provides a simplified picture of a program, initiative, intervention (or series of interventions) that is a response to a given situation. It shows the logical relationships among the resources that are invested, the activities that take place, and the sequence of changes that result. The results chain hierarchy is organized according to seven levels of results, which can be described as such:

- Level 7 represents the impact on an overall problem or ultimate goals.
- Level 6 represents changes to behaviours, practices, and actions of targeted individuals and communities.
- Level 5 represents changes to knowledge, abilities, skills, aspirations, and intended commitments of targeted individuals and communities.
- Level 4 represents reactions by targeted individuals and communities. Reactions include, for example, what participants and clients say about an initiative and their participation, their satisfaction and the perceived strengths or weaknesses of the initiative.
- Level 3 represents the engagement and participation of targeted individuals and communities.
- Level 2 represents an initiative’s activities and outputs.
- Level 1 represents the financial, human, physical and intellectual resources (i.e. inputs) which must go into a given initiative.

Underpinning the results chain hierarchy is the idea that initiatives can be thought of as taking place within concentric circles or spheres of influence. In the first sphere, the sphere of control,

---

6 Key stakeholder interviews were used to confirm this point.
resources are spent, activities are conducted and outputs are delivered. In this sphere, choices are made about how much to invest in activities and services and their respective intensity. Levels 1 – 3 of the results chain hierarchy are understood to be operating in this sphere of direct control. In the second sphere, the sphere of direct influence, it can be said that clients, intermediaries, partners or stakeholders are directly reached an initiative’s activities or services. The groups directly reached, and their reactions, use, knowledge, aspiration or behaviour changes represent the sphere of influence. Results hierarchy levels 3 – 6 are understood to be operating in this sphere. In the third sphere, the sphere of indirect or contributing influence, change is sought in broad communities. The results in this sphere tend to be related to an organization’s mission or an initiative’s ultimate goals. Levels 6 – 7 operate in this sphere.

Outcomes and Impacts of the MA 17 Clinical Trial
The outcomes and impacts of the MA 17 trial are summarized in the results hierarchy shown in Figure 3. Note that the hierarchy includes recommended results indicators developed by the Canadian Academy of Health Sciences (2009) as well as from other related work. They are organized according to the Society’s results chain hierarchy as interpreted by Valentim and Montague (internal work to the Society, April 2009). See Appendix A for a more detailed discussion on this framework and its development.

The highlights of Figure 3 include the following observations:

- Level 3 (engagement) – The MA 17 trial engaged a large and prestigious international group of researchers. This international engagement has fostered improved communication across groups and has heightened the CTG’s status in the international clinical trials research community. It has also increased the CTG’s ability to develop, mobilize and coordinate large international trials.

- Level 4 (reactions) – As a result of a high level of engagement, the CTG was invited to become a member of the US NCI clinical trials cooperative group program. There was also unprecedented media coverage of trial results.

- Level 5 (knowledge, attitude, skill and aspiration change) – New knowledge was generated about the role of aromatase inhibitors in adjuvant therapy, as evidenced through the publication list of the MA 17 trial. Nineteen publications in high impact journals and 28 abstracts were presented or published. Additionally, there was unprecedented recognition of trial performers (MA 17, Dr. Goss, CTG) by prescribing physicians.

- Level 5 (knowledge, attitude, skill and aspiration change) – The MA 17 trial showed the value of pursuing adjuvant breast cancer therapy beyond five years. This indicates a paradigm shift for research and clinical treatment.

- Level 6 (practice and behaviour change) – The primary trial results publication (Goss et al., 2003) is cited 721 times according to the Web of Science database. This high citation count indicates that trial results have informed a new research direction in late adjuvant therapy.

- Level 6 (practice and behaviour change) – The MA 17 trial was a success, demonstrating the value of aromatase inhibitors in treating postmenopausal women with HR+ early-stage breast cancer in the adjuvant setting. It established an aromatase inhibitor, letrozole, as a standard adjuvant therapy for breast cancer, following tamoxifen treatment. The trial of letrozole as an extended adjuvant therapy had essentially no ‘competitor’ technologies (while there were certainly other aromatase inhibitors in the marketplace there were none being used as an extended adjuvant therapy). A similar trial was started three years after MA 17, suggesting at least a three year lead over any similar work.
• Level 6 (practice and behaviour change) – The results of the MA 17 trial contributed to changing world-wide standard of care practices and are cited prominently in provincial, national and international guidelines for the adjuvant treatment of breast cancer. Based on trial results, adjuvant therapy for postmenopausal women with HR+ breast cancer is suggested to include an aromatase inhibitor in order to lower the risk of tumour recurrence. More specifically, Cancer Care Ontario, the British Columbia Cancer Agency, the Alberta Cancer Board, the National Comprehensive Cancer Network, and the American Society of Clinical Oncology guidelines all recommend aromatase inhibitors for women with HR+ breast cancer. The MA 17 trial is specifically cited in the recommended clinical practice guidelines of all these groups.

• Level 7 (end outcomes) – Evidence suggests that the MA 17 clinical trial was responsible for hundreds and possibly thousands of disease free years for Canadian women. It has almost certainly created thousands of disease free years worldwide. The data shows that approximately 1% (per year of use) of treated women will not suffer a breast cancer recurrence who otherwise would have had they not been treated with this therapy. The effect is of course cumulative. If 4,800 women per year were treated and continued treatment with letrozole and three years of impact was examined, using the efficacy data shown in Figure 2, over 150\(^7\) disease free survival years would be added by the use of letrozole. See section 6.0 for a more detailed discussion.

\(^7\) The data is gathered from the actual trial findings plus manufacturer data on prescriptions of letrozole to Canadian women in extended adjuvant settings similar to that of MA 17 in 2003-2004. This would not include any increase in usage beyond year 1, impacts on the use of other aromatase inhibitors or the effects on prescriptions outside of Canada. See section 6.0 for a detailed analysis.
### Chain of Results

| Measures of impact on overall problem, ultimate goals, side effects, social and economic consequences |
| Rate or incidence of cancer (incidence, mortality, morbidity) |
| Level of quality of life (Index TBD) |
| Level of advances in cancer science / research |

| Measures of adoption of new practices and behaviour over time |
| Level of research used (knowledge transfer, practice adoption) by scientists / policy makers / institutions / health care practitioners / consumers |
| Level of research used in curricula for new researchers (citation in text books and reading lists) |
| Level of research cited in ongoing health professional education material |
| Level of research cited in public policy documents |
| Level of research cited in advocacy publications |

### Outcomes and Impacts

- Reduced recurrence of breast cancer, which resulted in hundreds of disease free years for Canadian women
- Increased use of aromatase inhibitors in adjuvant therapy
- Increased international collaboration on hormone based breast cancer research

### 6. Practice & Behaviour Change

| Measures of individual and group changes in knowledge, abilities, skills and aspirations |
| Level of understanding of key related science information generated through research by scientists / policy makers / institutions / health care practitioners / consumers |
| Level of self-expressed commitment to specific areas of science / research or practice / protocol / policy change by scientists / policy makers / institutions / health care practitioners / consumers |
| Level of development of new knowledge in cancer research |
| Level of development of new methods in cancer research |
| Level of published research findings in a timely manner and in peer-reviewed journals with high “impact factors” |

### 5. Knowledge, Attitude, Skill and Aspiration Change

| What participants and clients say about the program; satisfaction; interest, strengths, and weaknesses |
| Level of program recognition and support from key stakeholders / target groups / participants |
| Level (volume, accuracy and ‘tone’) of media coverage of research and program activities |

### 4. Reactions

| The characteristics of program participants and clients; number, nature of involvement, and background |
| Level of engagement with other centers, networks, academic institutions, government agencies, etc. |
| Level of engagement by stakeholders / target groups / participants |
| Level of multidisciplinary and / or multisectorial research activities |
| Level of recruitment and retention of stakeholders / target groups / participants (e.g. junior investigators, researchers, review panelists, etc.) |
| Level of established external scientific advisory board(s) |

### 3. Engagement / Participation

| Implementation data on what the program actually offers |
| Level of research as per internal review guidelines |
| Extent to which plans, strategies, frameworks, etc. are delivered as per expectations (expected timelines, resource usage and quality levels) |
| Extent to which governance structure adheres to internal guidelines |
| Extent to which policy and financial decisions are made according to Board / Senior Management / Expert Advisory Committee(s) accepted guidelines and standards |
| Extent to which internal and external communication strategies adhere to internal standards and protocols / policies |

### 2. Activities & Outputs

| Resources expended; number and types of staff involved; time expended |
| Level of human resources (staffing) at all levels (according to norms, vacancies, expectations, benchmarks) |
| Level of financial resources (budgets vs. actuals) at all levels |

### 1. Inputs

| Level of CTG effort expended |
| $13 million from Novartis |
| $5 million per year from CCS |

---

**Figure 3.** MA 17 clinical trial outcomes and impacts organized according to the Society’s results chain hierarchy. The results chain hierarchy shows the relationship among the resources that are invested, the activities that take place, and the sequence of changes that result. The figure should be read from the bottom up and from left to right. The first column identifies the levels of results (1 – 7); the second provides a description of the levels of results; the third provides a set of generic indicators for each of the levels of results; and the fourth lists outcomes and impacts.**
specific to the MA 17 trial at each of the seven levels of results. Note that the MA 17 trial shows evidence of impact at all levels of the results hierarchy.

Research and innovation which preceded (and led) to the MA17 trial along with highlights of its results are traced over time in Figure 4. It shows that the Society funded endocrine research and the CTG organized other clinical trials in the time periods leading up to the MA 17 trial. It was not established that the Society-funded research or clinical trials conducted prior to the MA 17 were fundamental to the trial itself. Rather it can be said that through the funding of this research, the CTG and the Society forged important connections in terms of social networks and contributed to the scientific knowledge base and research capacity, which may have helped to undertake the MA 17 trial in the late 1990s.

In the late 1990s, during an era in which other therapies were favoured and no equivalent therapy was offered for extended adjuvant breast cancer treatment, principal investigator Dr Goss, through the CTG, was able to work with a large pharmaceutical company (recruited to the trial very late in the design) to carry out a trial involving the collaborative engagement and support of nine countries and 416 sites, which was an unprecedented trial of extended adjuvant therapy for breast cancer. At a mid-point review the trial was ‘unblinded’ due to the significant improvement in outcomes found in the review and women in the placebo group were given an option to take the therapy. A Canada-wide press release and a publication of the results in one of the world’s top rated medical journals, the New England Journal of Medicine (the New England Journal of Medicine had a rank of ‘1’ in citation ratings when recently reviewed), led almost immediately to observed changes in prescription practices in clinicians in Canada. The study also led to multiple ‘follow-on’ studies; both direct sub studies of the MA 17 trial and other related research.

The ‘burden’ in terms of cancer was certainly reduced in Canada and worldwide by this effort. The direct trial effect on disease free survival years is certainly in the hundreds in Canada and the thousands worldwide. In addition, the effect on the research paradigm in terms of adjusting the focus to include late to extended adjuvant endocrine therapy has been immeasurable.

Evidence also suggests that there are continuing implications for the work of the MA 17 trial as it has demonstrated the value of extending adjuvant aromatase inhibitor therapy in the treatment of women with HR+ breast cancer. The CTG went on to activate another trial in 2004, the MA 17R, which is a double-blind re-randomization to letrozole or placebo for women completing five years of adjuvant letrozole in the original MA 17 trial. Other similar trials to follow MA 17 include the NSABP B-42 and ABCSG16: SALSA, which also look at the use of aromatase inhibitors beyond a five year period and up to ten years. This signals a shift in thinking about the efficacy of aromatase inhibitors in the extended adjuvant setting; a setting in which no therapy, until recently, existed. This clearly demonstrates that the results of the MA 17 trial could continue to influence new research findings in the late to extended adjuvant therapy setting going forward.
Figure 4. Using the results chain hierarchy to trace the MA 17 trial over time along the R&D and innovation spectrum. Key activities and results are mapped both vertically according to the results chain hierarchy levels and horizontally across time and the R&D and innovation spectrum. The figure should be read from left to right and from the bottom up. This approach attempts to build in an appreciation of the multi-year build up of research which led to the MA 17 trial while showing the long-term impacts of the trial. As such, it recognizes the trial as part of a science and innovation pathway of connections.
6.0 Estimating Impacts of the MA 17 Clinical Trial

Given the context outlined in this report, the key estimation is to address health care impacts that relate to the Society’s mission. In this case, the calculation of impacts relates to two key items:

(i) the estimated efficacy of treatment
(ii) the estimated incremental or additional patients treated using letrozole (or another aromatase inhibitor) who we can estimate would not have been treated otherwise.

For item (i), for secondary (five year plus) letrozole treatment we can use the actual results of the MA 17 clinical trial. The following table lays out some basic calculations and rationale.

**Estimates of Letrozole Advantage Linear Regression Model**

<table>
<thead>
<tr>
<th>Year</th>
<th>Letrozole N</th>
<th>MinLimit</th>
<th>Placebo N</th>
<th>MaxLimit</th>
<th>ActDiff</th>
<th>MinDiff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S 95% CI</td>
<td></td>
<td>S 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2425</td>
<td>0.985</td>
<td>2409</td>
<td>0.979</td>
<td>0.985</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.981</td>
<td></td>
<td></td>
<td></td>
<td>-0.004</td>
</tr>
<tr>
<td>2</td>
<td>1555</td>
<td>0.969</td>
<td>1530</td>
<td>0.954</td>
<td>0.963</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.961</td>
<td></td>
<td></td>
<td></td>
<td>-0.002</td>
</tr>
<tr>
<td>3</td>
<td>768</td>
<td>0.957</td>
<td>723</td>
<td>0.922</td>
<td>0.936</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.948</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>4</td>
<td>244</td>
<td>0.944</td>
<td>231</td>
<td>0.898</td>
<td>0.918</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
</tbody>
</table>

*These calculations are based on Figure 2 in the case study write up and the reported Kaplan-Meier curve and survival 'S' % per year both before and after study unblinding, which suggests that the letrozole effect is between just over half of one percent (.006) as a minimum (confidence level 95%) and a 'best estimate' of almost 1.5%. Note 'best' does not mean most optimistic, but rather most likely.

From the above, it can be concluded that the additional prescription of letrozole as adjuvant therapy in conditions similar to those of the MA 17 trial would have a significant effect on reducing cancer recurrence. That difference can be modestly estimated in the 1% per year area, especially if only 3 years of effect are considered. As done by a full blown cost-effectiveness analysis (Delea, Smith & Brandman, 2006) the actual study findings will be used to estimate efficacy.

**Best Fit linear equation to estimate the yearly effect on reduced incidence of letrozole**

\[ y = mx + b \]

Where:

- \( y \) = estimated letrozole effect
- \( m \) = slope
- \( x \) = time (years)
- \( b \) = intercept

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Less</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0045</td>
<td>0.006</td>
<td>0.0015</td>
</tr>
</tbody>
</table>
**Estimates of Letrozole Advantage Linear Regression Model**

| 0.0185 | 0.015 | 0.0035 |
| 0.0325 | 0.035 | 0.0025 |
| 0.0465 | 0.046 | 0.0005 |

Average estimating error using the above 0.002

Conclusion: The best fit linear equation will do for estimating the effects of letrozole in MA 17 protocol conditions, given a 'short' estimating time period, for broad purposes of estimating disease free years.

For item (ii), for a conservative estimate we can take the number of years which MA 17 can be estimated to have advanced the introduction of an aromatase inhibitor for extended adjuvant therapy and find best estimates of the number of women who fit that profile (i.e. post menopausal, five years plus since surgery) treated in those years.

In terms of estimating the incremental years of impact, a reasonable advance to use can be estimated as three years given the lack of alternatives at the time and the conditions in the marketplace. (Note: the standard time period being considered in US National Science Foundation (NSF) case studies according to Jordan (2009) has apparently been five years. As such, the study team is comparatively conservative in this estimate of three years. Recent work by the UK’s National Health Service (2006) has suggested that impact estimates for clinical trials have been taken for 10 years. See Appendix A for a more detailed discussion on estimating the impacts of health research.

For an estimate of the number of women treated, and failing definitive registry sources, we took estimates from clinical guidelines experts and records of company sales (i.e. Novartis). The following chart summarizes the data supplied by Novartis.

**MA 17 Clinical Trial Impact on Total Prescriptions (TRx) of Letrozole**

Source: IMS Ferrara TRx data adjusted for TRx capture rate Jun 2009
Figure 5. Total prescriptions (includes new prescriptions and refills) of Letrozole prior to the MA 17 clinical trial unblinding and one-year post MA 17 clinical trial unblinding. Key dates related to the trial are also highlighted along the timeline.

Key Assumptions:
- MA17 study DSMC unblinded the data and the communication to trialist and patients commenced in Oct 2003.
- Data presentation took place in SABC Dec 2003.

<table>
<thead>
<tr>
<th></th>
<th>Oct-03</th>
<th>Nov-03</th>
<th>Dec-03</th>
<th>Jan-04</th>
<th>Feb-04</th>
<th>Mar-04</th>
<th>Apr-04</th>
<th>May-04</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRx Actual</td>
<td>4474</td>
<td>4597</td>
<td>5529</td>
<td>5339</td>
<td>5272</td>
<td>6281</td>
<td>6292</td>
<td>6863</td>
</tr>
<tr>
<td>TRx Projected with Pre-MA17 trends</td>
<td>3989</td>
<td>4038</td>
<td>4087</td>
<td>4137</td>
<td>4186</td>
<td>4236</td>
<td>4285</td>
<td>4335</td>
</tr>
</tbody>
</table>

Estimated Number of Extended patients treated with letrozole: 3414*
Estimated Number of Extended patients in Canada: 8750
Patient Penetration: 39.0%

*Note that this number needs to be added to the number of patients being prescribed letrozole as part of the clinical trial (estimated as 1,400 Canadians) rendering a total estimate of 4,800 Canadians (approximately)

The use of these estimates gives us a conservative estimate of disease free years directly influenced by MA 17 as follows:

<table>
<thead>
<tr>
<th>Years of Treatment</th>
<th>Recurrence Avoided</th>
<th># Treated*</th>
<th>Disease Free Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.006</td>
<td>4,800</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>.015</td>
<td>4,800</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>.035</td>
<td>4,800</td>
<td>168</td>
</tr>
<tr>
<td>4</td>
<td>.046</td>
<td>4,800</td>
<td>221</td>
</tr>
<tr>
<td>5</td>
<td>.06</td>
<td>4,800</td>
<td>288</td>
</tr>
</tbody>
</table>

* This number was estimated for one year in Canada by the manufacturer of letrozole. Note that if all aromatase inhibitors were included and some growth in the number of prescriptions was assumed the number could be significantly larger. If the number of prescriptions worldwide were included the number of disease free years estimated would certainly be in the thousands.

Note that the range of estimates above only relates to disease free years directly and clearly (very plausibly) attributable to the MA 17 trial and its direct application. The less direct impacts, for example the benefits of other late to extended adjuvant therapies brought forward more quickly because of the MA 17 trial, cannot be realistically estimated.

Economic impacts are not calculated here as they are both difficult (requiring sophisticated modeling) and are not directly indicative of the Society mission. The most recent and directly applicable cost-effectiveness study done (Delea et al., 2006) suggested that the use of letrozole in the MA 17 protocol was a cost-effective therapy in terms of disease free survival and in terms of quality adjusted life years, even when including negative effects. Quality adjusted life year cost estimates averaged under $30,000 in model estimations and were under $50,000 in 94% of the probabilistic sensitivity analysis scenarios modeled. This puts the therapy well within acceptable cost-effectiveness norms. The authors noted that cost-effectiveness levels might improve once the longer term effects of extended treatment are made available (these estimates were based on only 3 years of aromatase inhibitors use and associated risk reduction).

Other Considerations

As noted in section 7, while disease free years directly attributable to the MA 17 trial are one tangible and quantifiable result, the biggest effects over the long term appear to relate to three areas:
1. The nature of collaboration across borders in trials of this nature. MA 17 has led to other multinational studies looking at the use of aromatase inhibitors in the late to extended adjuvant setting.

2. The leadership of the CTG in running large multinational trials with the direct participation of other North American and European groups. MA 17 has allowed CTG to gain access to informational and financial support of the US NCI clinical trials cooperative group program. This greatly enhances the ability of CCS funding to get ‘leveraged’ into making a difference in the future.

3. The nature of adjuvant endocrine therapy research (specifically the time horizons for adjuvant therapies) has permanently changed. This undoubtedly means thousands of women’s lives will be affected for the better.

7.0 Incrementality

The circumstances noted above suggest that the MA 17 trial was incremental to hormone based breast cancer research in terms of both ‘project’ (i.e. to what extent would this trial have been done otherwise) and in terms of ‘marketplace’ (i.e. to what extent would other groups have moved in to do this work and achieve these outcomes).

In terms of project incrementality, it is quite unlikely that Dr Goss, while clearly a resourceful and determined proponent for the project would have been able to establish the MA 17 trial elsewhere. Especially in North America, where historically there had been treatment bias in favour of chemotherapy that made it difficult to conduct trials associated with breast cancer hormone treatment therapies. In fact, this was not the first trial that Dr Goss had proposed to the CTG and the MA 17 trial was only approved by the CTG after a close vote. Also, the fact that the original industry partner withdrew before the trial was activated and Novartis was skeptical regarding the eventual trial outcome (as recalled by interviewees) makes it even more unlikely that the MA 17 trial would happen elsewhere.

In terms of marketplace incrementality, a number of adjuvant trials using aromatase inhibitors were activated directly after or at around the same time as the MA 17 trial. However, only one such trial, the NSABP B-33, was assessing use of an aromatase inhibitor beyond five years of initial adjuvant tamoxifen therapy like the MA 17 trial. The NSABP B-33 was stopped because of the MA 17 trial suggesting that the use of an aromatase inhibitor as an adjuvant therapy would definitely have been tested and likely ‘confirmed’ soon after MA 17 released its results. This means that the ‘window’ of impact for the MA 17 trial on the use (prescription) of letrozole was about two or three years. In the vernacular of current cost-benefit studies (Jordan, 2009) there was a ‘defender’ technology for letrozole for adjuvant therapies up to five years, (tamoxifen and/or aromatase inhibitors) but there was no competitor as yet for post 5 year adjuvant therapies. Therefore, it can be argued that the MA 17 trial helped create a new therapy ‘marketplace’. This

---

8 The evidence for the circumstances surrounding the likelihood of the trial proceeding without the CTG is now largely in the memories of participants a dozen years after the fact. This being the case, there remains strong circumstantial evidence that this trial (or another like it) would not have occurred in this time frame.

9 Other trials were assessing the aromatase inhibitors as initial adjuvant therapy or the sequential use of aromatase inhibitors during initial five years of adjuvant endocrine therapy.

10 Literature shows that the NASBP B-33 was initiated in 2001 and then terminated in 2003. This means that it began at least two years after the MA 17 trial. Therefore, the results can be ‘incremental’ for a minimum of two years. Further interviews actually suggested a three year difference. Two other factors might make it even more incremental: 1) the fact that MA 17 was unblinded midway through (a rarity) means that the MA 17 trial might actually have been another 2.5 years ahead of NASBP B-33 (if it was not also stopped midway through as well); 2) It was suggested by key informants that the launch of the MA 17 trial two years earlier may have influenced the decision to initiate the NASBP B-33 trial (i.e. the MA 17 trial may have broken the “barrier” to conducting extended adjuvant trials and as such the NASBP B-33 became possible.)
may be the most important ‘incremental’ impact of the trial, especially as it relates to disease free survival outcome.

8.0 Barriers Overcome by the MA 17 Clinical Trial

While research, discovery and innovation move quickly in the pharmaceutical cancer treatment sector (largely due to the potential lucrative rewards) the costs are very high and there can be biases built into the system. Several biases and / or barriers seem to have been in place at the time of the MA 17 trial, which had to be overcome by the trial study.

Treatment Bias in Favour of Chemotherapy – The largest provider of pharmaceuticals and the biggest proximate market to Canada is the United States. As suggested by key informants, until the turn of the 21st century the bias in the marketplace had been to favour chemotherapy over hormone therapy in the adjuvant therapy setting in the United States. Earlier efforts to investigate hormonal solutions (even in Canada where expertise had been developed) were not always met with positive responses.

Time Bias – Interviewees noted that there was a tendency to fund drug trials for periods of time that were not always optimal. This could be attributed to the expensive nature of clinical trials and/or the general nature of the marketplace. Interviewees indicated that drug manufacturers are most interested in gaining marketplace approvals (i.e. US Food and Drug Administration, Health Canada) and are often reluctant to fund trials which go beyond a certain period of time in the adjuvant therapy setting. Another explanation for the bias may be that at the time of the MA 17 trial, norms of practice had not caught up to the reality of the large numbers of five year plus breast cancer survivors and the fact that, notwithstanding the survival improvement, there was a significant risk of recurrence after five years of adjuvant tamoxifen treatment.

Gaps in Sharing – Up until the MA 17 trial, it is suggested by interviewees and a review of the literature that there had rarely been much in the way of international clinical trials in this area of cancer treatment. Certainly for the CTG, this trial was the first large scale multinational trial it had lead. Given the gap in sharing, pre-existing biases in terms of favouring chemotherapy and limited time, treatments might have been prolonged.

The Strength of Weak Ties – The evidence reviewed for this case study suggests that the MA 17 trial was the first extended adjuvant endocrine therapy phase III trial led by the CTG. Furthermore, while the Society had previously funded areas of research related to the MA 17 trial (i.e. hormone based breast cancer research) it cannot be said that the Society had placed a major funding focus in this area 11. Almost counter-intuitively, these factors may have played an important role in the successful launch and conduct of the MA 17 trial.

In the field of social network analysis, analysts such as Granovetter (1973) and Burt (2000) have suggested that, counter to popular biases favouring tightly connected networks, it is in fact groups that have a number of weak ties that can achieve the most success. This is especially true in areas such as innovation (Borgatti, 2005). For the CTG it may be that its weak ties across research interests and across sectors may have helped it to both overcome inadvertent bias (i.e. to make groups aware of information they would not normally have focussed on) and conscious bias (e.g. beliefs causing a focus on early vs. late or extended adjuvant therapy, chemotherapy vs. hormone therapy etc.). The fact that the Society had provided some funding to the area of endocrinal therapies for breast cancer, but had not specialized in it may have also helped the CTG maintain credibility in brokering the biggest trial which had ever been done up to that time in this area.

11 An extensive review of past Society funding suggests a connection, but not a prime focus.
9.0 Observations and Recommendations

The strategic implications for the Society as demonstrated by this case are as follows: there is value in funding a clinical trial group which has built up a long-term reputation, provides researchers with access to wide regional trial opportunities in addition to world class management expertise and in many respects can act as independent broker among the various interests and potential biases surrounding cancer treatment. In other words, there appears to be great value in a research group which places value in the mission to defeat cancers above loyalty to research agendas, institutions or geographic regions.

One area which would appear to show potential for improvement is in the tracking of the actual take-up and use of research. This was found to be difficult in this case study, a situation in which this trial was clearly successful. Given this experience, the team concludes that tracking take-up and use of research would be even more difficult for other types of research funded by the Society. There would appear to be a need to place a stronger emphasis on the knowledge translation elements of innovation in terms of tracking Society investments through to changes in research, policy and individual practice. This, however, leads to the larger question regarding the Society’s role in the knowledge translation of the research it funds. More specifically, beyond the tracking of research use and take-up, what should the Society’s role be in translating the knowledge generated through its funded research from the research setting into real-world applications?
References


Appendix A: Estimating the Impacts of Health Research
Estimating the Impacts of Health Research

Background

Evaluators have struggled for decades to develop approaches and metrics to estimate the impacts of research, development and technological innovation. (See forthcoming Research Evaluation, 2010). In the area of health research, science and innovation the current 'state of the art' may be summarized as being embodied in the work of the Canadian Academy of Health Sciences (CAHS) Making An Impact A Preferred Framework and Indicators to Measure Returns on Investment in Health Research, 2009. This publication is summarized below.

The goal of this work is to provide a practical framework, including a system of metrics, which can provide transparency and accountability to funders. The work has spawned further social science research such as that led by Dr Jerald Hage of the University of Maryland for the NSF. The purpose of this ongoing research is to evaluate this metric system on a series of dimensions: (1) the ease of using the system, (2) the scope of its application, and (3) the utility for developing a permanent monitoring system. The metrics are expressed in a standardized form as percent change so that they can be applied to any treatment problem or morbidity, genetic defect (alpha minus one deficiency), injury (post-traumatic stress syndrome), illness (breast cancer), and degenerative process (Alzheimer’s disease) in any of the different Institutes of Health. But the ease in employing the metrics supposes the ability to determine the standards or norms on which the percent changes would be computed. For example, a new treatment protocol for stage four melanoma may result in a research finding that it can extend the duration of life for two months in 30 percent of the cases that is the success rate of the intervention in Figure B1. Measuring the percent change requires knowing the expected duration of life for this specific population (stage four melanoma). If the new treatment only impacts 30 percent of the specific patient population, then the economic value of this gain must be weighted accordingly. To obtain this information the study team intends to work closely with the appropriate staff at the US National Institutes of Health (NIH). Another aspect of testing this system is the assessment of the quality of the information in the research proposals and progress reports. In particular, how often does research on the basic knowledge, the last three metrics in Figure B1, relative to a specific morbidity, report the implications of their findings for any of the clinical indicators listed? Finally, the measure of utility is essentially how useful the specific Institutes of Health find this list of health care impacts and their economic consequences and whether they perceive that this could form the basis of a permanent monitoring system, an issue that is actively being discussed at present.
### Figure B1: Health Care Impacts

**Prevention (percent decline in)**
- incidence of morbidity (see Kolata, 2008)
- severity of incidence of morbidity

**Intake and Assessments (percent increase)**
- speed of diagnosis
- accuracy of diagnosis (reduction in false positives or negatives, see Miller, 2008)
- accuracy of prognosis (duration and quality of life, etc.)

**Treatment Interventions (percent decreases in)**
- wait time in the emergency room
- length of treatment
- side-effects of intervention and/or their severity
- opportunistic infections during treatment intervention

**Treatment Interventions (percent increase in)**
- quality of life during treatment QALYs (fewer invasive procedures, opportunities to be outpatient, reduction in pain, etc.)
- success rate of intervention

**Post-Treatment Interventions (percent increase in rehabilitation and long term care metrics)**
- reduction in waiting time for rehabilitation intervention
- reduction in length of rehabilitation and long-term care
- quality of life during rehabilitation and after care (decrease in the pain of rehabilitation procedures, reduction in invasive procedures, opportunities to be treated as an outpatient).
- success rate of rehabilitation (DALYs) or increase in physical (vision, hearing, thinking, movement, dexterity) and psychological functioning (cognitive processing, speech, memory) after stroke or injury that impaired functioning

**Summary Output Measures of the Morbidity Sector (percent increase in)**
- average duration of life given the morbidity (QALYs)
- quality of life or health status after interventions (reduction in recurrences, continuity in mobility, reduction in constraints of life style, etc.)

**Knowledge about the Health Care Problem (percent increase in)**
- understanding of the causes of the health care problem
- number of sub-categories of the health care problem
- understanding of the relevant biological and psychological processes

---

### Figure B2: Economic Benefits from Health Care Impacts

**Prevention (value of changes in morbidity)**
- illness days saved from decline in morbidity incidence
- reduction in cost of treatments for less severe morbidity incidence

**Intake and Assessments (reductions in costs of)**
- tests for diagnosis
- false positives or negatives
- futile interventions

**Treatment Interventions (reductions in costs)**
- waiting time for treatment
- treatment days saved (e.g. hospital days)
- side-effects of intervention and/or their severity that have been eliminated
- opportunistic infections eliminated during treatment intervention

**Treatment Interventions (valued added)**
- quality of life during treatment
- because of less invasive procedures, shift from hospital to outpatient

**Post-Treatment Interventions (value of rehabilitation and long term care improvements)**
- days saved in waiting time
- days saved in rehabilitation and after care
- reductions in treatment costs because of less invasive procedures, shift from rehabilitation hospital to outpatient care
- increased mobility of all kinds after rehabilitation

**Summary Output Measures of the Morbidity Sector (value added)**
- increase in the average duration of life given the morbidity
- increase in health status (absence of reoccurrence or saved health care costs and increase in the quality of life after interventions)
The Canadian Cancer Society Approach: A Complement and Contrast

The work of this case study can be seen to be a complement to the NSF assignment. Though it is a considerably more modest effort, the MA 17 case study has been designed to seek out information on all relevant areas of the Figure B1 checklist on health care impacts. To a lesser extent, some attention can be paid to the Figure B2 list of economic effects.

The key difference (aside from the level of resourcing to pursue impacts and the scale of efforts) between the orientation of this MA 17 case study and the 25 case studies being studied for the NSF is three fold:

1. The Society approach is focused on an agreed hierarchy of results with mission ends at the top. In other words, the case is intended to demonstrate a direct connection to the eradication of cancer (prevention and / or diagnosis and treatment and / or quality of life of those living with cancer). These outcomes are clearly set as the prime concern.

2. The Society approach attempts to use a structured hierarchy of results to describe the performance story in the case study. Figure B1 (and to a lesser extent Figure B2) metrics are placed within a results hierarchy or ‘chain’ framework which is intended to help explain a causal sequence. This is very consistent with emerging theory of change archetypes (Ottoson & Hawe, 2009).

3. The Society approach attempted to build in an appreciation (to the extent possible) of the multi-year build-up of research and innovation support which led to the MA 17 trial. Recognizing the trial as part of a science and innovation pathway of connections. Such a lens, while always acknowledged as a fundamental part of any innovation story, is relatively new in evaluation work seeking to demonstrate attributable impacts to given investments (see Jordan, 2009 on ‘cluster’ cost-benefit approaches to innovation).

The conceptual ‘model’ for this framework is contained in Figure B3. Note that this original model comes from the US Centers for Disease Control and Prevention (CDCP) and the adapted Society version Figure B3A reflects key elements of the CAHS categories. It is the contention of the authors of this case report that the placement of results and indicators in this fashion enhances the impact and attribution theory of the case. In other words, by examining the hierarchy one should be able to apply ‘if’ ‘then’ logic to string together a theory of change. The more check points on the results chain that can be found the more plausible the case that the project made a truly ‘incremental’ contribution to a mission end outcome. For example, we can suggest that the almost unprecedented linkage of North America and European groups in the MA 17 trial demonstrated ‘incrementality’ by fact of its newness leading us to believe that the successful conduct of the trial and the credibility of its results were greater. The high citation of the trial’s primary publication by a diverse set of health care stakeholders, including practitioners, leads us to believe that the trial had extraordinary implications for health care delivery. Finally the documented change in prescription levels makes a compelling case that the MA 17 trial was incremental.

In addition to the hierarchy, the extended time investigation of the approach used here lends credibility to assertions about the incremental impact which MA 17 had in the breast cancer adjuvant therapy ‘marketplace’. Project files, interviews and the literature all suggest that the NCIC (now CCSRI) contributed to hormone-related (endocrinal) breast cancer research for decades prior to the MA 17 trial and fostered both a strong connection among some of the key proponents (e.g. Dr Goss, Dr Pritchard and others) and an understanding and appreciation for the use of hormone-related treatments in adjuvant

\[12\] Incrementality (sometimes called ‘additionality’) is a concept which is critical to impact assessment. It can be considered as taking place at two levels. First, incrementality at a project level can be considered to address the question of “would this project have occurred without assistance?” In this case, it is a question of whether the MA 17 trial would have gone ahead (and in what fashion) without CTG assistance. The second part of incrementality relates to the marketplace. The question on this second level is “would something similar have taken place (and in what fashion) if MA 17 had not occurred?” Section 7 of the report addresses both these points.
circumstances (interviews suggest that chemotherapy had been favored in the United States up until the mid to late 1990s).

The structured analysis of this case study suggested that MA 17 made a strong contribution to the Society mission. The next section discusses the level of that impact.

**Figure B3: Conceptual ‘Model’**

US CDCP Example:

For programs with complex public health problems, the ultimate outcome is often ambitious and long term... hence a strong program description usually provides details not only on the intended long-term outcomes but the short-term and intermediate outcomes that precede it and the sequence in which they are likely to occur...

Evaluations are strengthened by showing evidence at several levels of hierarchy; information from the lower levels helps to explain results at the upper levels, which are the longer term.


Note that the model used by the CDCP for their own evaluation guidance refers to a hierarchy that is very similar to that shown in section 7 (Figure 3) of the main report and repeated on the following page.
Figure B3A: MA 17 Clinical Trial Outcomes and Impacts Organized by the Canadian Cancer Society Results Hierarchy

<table>
<thead>
<tr>
<th>Initiative Chain</th>
<th>Hierarchy of Evaluation Criteria / Evidence</th>
<th>Typical Indicators</th>
<th>Outcomes and Impacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. End Outcomes</td>
<td>Measures of impact on overall problem, ultimate goals, side effects, and economic consequences</td>
<td>✓ Rate of incidence of cancer (incidence, mortality, morbidity) – Level of quality of life (Index TBD) ✓ Level of advances in cancer science / research</td>
<td>• Reduced recurrence of breast cancer, which resulted in hundreds of disease free years for Canadian women • Increased use of aromatase inhibitors in adjuvant therapy • Increased international collaboration on hormone based breast cancer research</td>
</tr>
<tr>
<td>6. Practice &amp; Behaviour Change</td>
<td>Measures of adoption of new practices and behaviour over time</td>
<td>✓ Level of research used (knowledge transfer, practice adoption) by scientists / policy makers / institutions / health care practitioners / consumers – Level of research used in curricula for new researchers (citation in text books and reading lists) ✓ Level of research cited in ongoing health professional education material ✓ Level of research cited in public policy documents ✓ Level of research cited in advocacy publications</td>
<td>• Adherence to new protocols by practitioners regarding extended adjuvant therapy options • Changed timeframe for adjuvant therapy research • Increased number of clinical trial using aromatase inhibitors in the adjuvant setting • New standard for adjuvant therapy (use of aromatase inhibitors and longer term adjuvant treatment) • Trial results cited in provincial, national and international clinical practice guidelines • Primary trial publication (Goss, 2009) cited 721 times (WOS, 2010)</td>
</tr>
<tr>
<td>5. Knowledge, Attitude, Skill and Aspiration Change</td>
<td>Measures of individual and group changes in knowledge, abilities, skills and aspirations</td>
<td>✓ Level of understanding of key related science information generated through research by scientists / policy makers / institutions / health care practitioners / consumers ✓ Level of self-expressed commitment to specific areas of science / research or practice / protocol / policy change by scientists / policy makers / institutions / health care practitioners / consumers ✓ Level of development of new knowledge in cancer research ✓ Level of development of new methods in cancer research ✓ Level of published research findings in a timely manner and in peer-reviewed journals with high “impact factors”</td>
<td>• Increased interest in late to extended adjuvant therapy research • Demonstrated value of pursuing adjuvant breast cancer therapy beyond five years • Unprecedented recognition of trial performers (MA 17, Dr Goss, CTG) by prescribing physicians • 19 publications in high impact journals including the New Journal of Medicine and Journal of Clinical Oncology; 28 abstracts presented or published • CTG invited to become a member of the US NCI clinical trials cooperative group program • Unprecedented media coverage of trial results; widely reported press release • NSABP B-33 trial is stopped due to the MA 17 trial results</td>
</tr>
<tr>
<td>4. Reactions</td>
<td>What participants and clients say about the program; satisfaction; interest, strengths, and weaknesses</td>
<td>✓ Level of program recognition and support from key stakeholders / target groups / participants ✓ Level (volume, accuracy and ‘tone’) of media coverage of research and program activities</td>
<td>• A Canada-wide joint press release (CCS, US NCI, PMH) on the trials result / trial unblinding at the time of the first interim analysis as recommended by the CTG’s DSMC • Higher than projected patient accrual • Involvement of international groups like SWOG, ECOG, CALGB, NCCTG, EORTC, IBCSG • Trial unblinding at the time of the first interim analysis as recommended by the CTG’s DSMC • Prompt communication of trial results to patients, physicians and the research community • Trial funding and management according to CTG standard operating procedures and policies • Use of stringent trial protocols (quality assurance) developed by the CTG in collaboration with external experts and partners</td>
</tr>
<tr>
<td>3. Engagement / Participation</td>
<td>The characteristics of program participants and clients; number, nature of involvement, and background</td>
<td>✓ Level of engagement with other centers, networks, academic institutions, government agencies, etc. – Level of multisciplinary and / or multisectorial research activities ✓ Level of recruitment and retention of stakeholders / target groups / participants (e.g. junior investigators, researchers, review panelists, etc.) – Level of established external scientific advisory board(s)</td>
<td>• CTG invited to become a member of the US NCI clinical trials cooperative group program • Unprecedented media coverage of trial results; widely reported press release • NSABP B-33 trial is stopped due to the MA 17 trial results</td>
</tr>
<tr>
<td>2. Activities &amp; Outputs</td>
<td>Implementation data on what the program actually offers</td>
<td>✓ Level of research as per internal review guidelines – Extent to which plans, strategies, frameworks, etc. are delivered as per expectations (expected timelines, resource usage and quality levels) ✓ Level of engagement by stakeholders / target groups / participants ✓ Level of multidisciplinary and / or multisectorial research activities ✓ Level of recruitment and retention of stakeholders / target groups / participants (e.g. junior investigators, researchers, review panelists, etc.) – Level of established external scientific advisory board(s)</td>
<td>• A Canada-wide joint press release (CCS, US NCI, PMH) on the trials result / trial unblinding at the time of the first interim analysis as recommended by the CTG’s DSMC • Prompt communication of trial results to patients, physicians and the research community • Trial funding and management according to CTG standard operating procedures and policies • Use of stringent trial protocols (quality assurance) developed by the CTG in collaboration with external experts and partners • Level of CTG effort expended • $13 million from Novartis • $5 million per year from CCS</td>
</tr>
<tr>
<td>1. Inputs</td>
<td>Resources expended; number and types of staff involved; time expended</td>
<td>✓ Level of human resources (staffing) at all levels (according to norms, vacancies, expectations, benchmarks) ✓ Level of financial resources (budgets vs. actuals) at all levels</td>
<td>• Level of CTG effort expended • $13 million from Novartis • $5 million per year from CCS</td>
</tr>
</tbody>
</table>
References


Appendix B: Methodology, Limitations & Lessons Learned
A case study methodology was employed and the Canadian Cancer Society results hierarchy was used as an organizing structure to describe the inputs, activities and sequence of impacts which occurred before, during and after the MA 17 trial.

The steps in this process were as follows:

<table>
<thead>
<tr>
<th>Summary of Case Study Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Undertake a targeted review of the scientific literature to provide an accurate history of the science and how its uptake has been supported by the medical community. A timeline of key letrozole resources resulted from this review and stakeholder contributions were identified where possible.</td>
</tr>
<tr>
<td>2. Assemble profile of:</td>
</tr>
<tr>
<td>a. History of aromatase inhibitors (especially letrozole) as an adjuvant treatment for female HR+ breast cancer patients (key literature); pre and post clinical trial supported by the Society.</td>
</tr>
<tr>
<td>b. Clinical trial supported by the Society – why, how, who, when and what are the results (NCIC and CTG files)</td>
</tr>
<tr>
<td>3. Consult with Dr Goss for:</td>
</tr>
<tr>
<td>a. Contextual history and general terms of the clinical trial as well as use and take-up of trial results</td>
</tr>
<tr>
<td>b. Names / contact info for key persons and institutions which we can pursue to verify use of trial results</td>
</tr>
<tr>
<td>c. Other related information (e.g. any key precursor research to this therapy which was connected to / funded by the Society through the NCIC?)</td>
</tr>
<tr>
<td>4. Contact other key informants as identified by CCSRI, CTG, Dr Goss and the literature. Final interview list included: Dr Wosnick, CCSRI; Dr Williams, CCSRI; Dr Shepherd, CTG; Dr Pater, Cancer Care Ontario; Dr Goss, Massachusetts General Hospital; Dr Ingle, Mayo Clinic; Dr Pritchard, Sunnybrook Health Sciences Centre; Dr Grunfeld, Ontario Institute for Cancer Research; Mr. Martens, Novartis</td>
</tr>
<tr>
<td>5. As available, seek out and analyze cancer database evidence (e.g. from cancer registries) regarding actual use of letrozole over time and in what circumstances. (This was not found to be available and manufacturer data was substituted).</td>
</tr>
<tr>
<td>6. Review cost-effectiveness evidence (e.g. US and UK cost-effectiveness studies) and build cost-effectiveness estimates (including a full consideration of additionality) based on the Canadian trial and Canadian circumstances (referencing Jordan cost-effectiveness / cost-benefit approach, 2009) Also review other Canadian sources regarding costs and use. (Methodology of benefits ‘time advance’ reviewed with Jordan and Hage – general analysis used for broad estimates)</td>
</tr>
<tr>
<td>7. Draft case study for review</td>
</tr>
<tr>
<td>8. Review (in-house and by experts)</td>
</tr>
<tr>
<td>9. Revise and distill lessons learned for future applications</td>
</tr>
</tbody>
</table>

**List of Interviewees**

The following 9 individuals were interviewed in the course of developing the case study:

Dr Paul Goss, Massachusetts General Hospital Cancer Centre  
Dr Kathleen Pritchard, Sunnybrook Health Sciences Centre  
Dr Joseph Pater, Cancer Care Ontario  
Dr Eva Grunfeld, Ontario Institute for Cancer Research  
Dr Lois Shepherd, National Cancer Institute of Canada Clinical Trials Group
Dr James Ingle, Mayo Clinic
Mr. Jeff Martens, Novartis Pharmaceuticals Canada Inc.
Dr Michael Wosnick, Canadian Cancer Society Research Institute
Dr Christine Williams, Canadian Cancer Society Research Institute

Limitations:

The limitations of this case study can be considered in two categories:

1. General limitations related to R&D and innovation case studies.
2. Limitations specific to the circumstances of this case.

General Limitations
The evaluation of research, technology, development and innovation is inherently difficult (Ruegg & Feller, 2003). The results flow of R&D and innovation is, by definition, not very predictable, not easily ‘benchmarked’, subject to constant change and usually involve a multitude of contextual and relationship factors. R&D and innovations typically take place over long time periods producing often intangible results in terms of information, knowledge and insight. For these reasons R&D and innovations are not readily quantifiable in terms of either their costs or benefits. As a result of the above factors, they are inherently difficult to describe in terms of discrete, attributable impacts.

Specific Limitations
The time frame of coverage for this assessment was a long one (as noted above, this is typical for an R&D and innovation case) and necessarily so as it had to do with a somewhat long term effect. None-the-less key events in this case happened 7 to 12 years prior to collection and it is difficult to ‘recreate’ the exact circumstances regarding just who did what with whom and why.

The ‘third party’ delivery CTG funding (i.e. the Society funding the CTG through the NCIC (now CCSRI)) and the unavailability of some records to the study team presented some limitations. (For example, the record of decision making regarding the approval of the MA 17 trial by the CTG would have been useful, but was not made available\(^\text{13}\)).

From a results perspective, beyond the obvious limitations in terms of team resources to pursue all potential impacts (the qualitative impact assessment alone of case studies done in the US and elsewhere in related areas would dwarf the entire time and resource budget of this effort), lack of available cancer registry data or other sources on actual prescriptions hindered the development of strong results information. There appears to be a strong bias in the system towards using market regulator approvals and publications / citations as results metrics. From there cost-effectiveness estimates appear to ‘assume’ levels of use and take-up when modeling costs and benefits. (The three cost-effectiveness studies reviewed made fairly sweeping assumptions about take-up and appropriate use even though interview and some literature review evidence suggest that this cannot be taken for granted.)

While publications, citations and regulatory approvals are certainly results that are worth noting the most important results for the Society involve the actual take-up and application of innovations by target communities leading to a reduced burden and / or improved quality of life. The dearth of evidence tracking in this area even for what was deemed a great success (one wonders if any evidence would be available for use / take-up verification if the innovation was deemed only a moderate success) suggests that significant future work is needed in this area.

Lessons Learned:

Some important lessons learned reinforced by this project include the following:

\(^{13}\) It was not available because it was not present in the CTG archives.
1. A full spectrum review of innovation from research through to actual (verified) use in target communities is warranted. In other words, there is value in addressing the full research and development (R&D) and innovation spectrum over time.

2. Simplifying assumptions about knowledge translation into use should be used with extreme caution. This includes assumptions about take-up level, compliance to therapy regimes and the timing for estimating benefits (this particular case took particular care to try to estimate the ‘advance’ in therapy realistically). In fact, this case shows a need to improve the tracking and monitoring of knowledge translation into practice of Society funded research.

3. Considerations of context, situation, collaborative and competitive environments are critical. Several important insights were gained by addressing the context and conditions surrounding the MA 17 trial. These include research trends, the nature of the key stakeholders (e.g. medical oncologists tend to follow the direction of credible research more so than some other areas of clinical practice) and the social networks which may help explain results.

4. An understanding of the fields of knowledge diffusion, utilization, transfer and translation would seem to be useful in explaining and understanding a research story such as the MA 17 trial (see Ottoson & Hawe, 2009).

5. It appears that the adapted results hierarchy developed and tested here by Valentim and Montague provides a useful structure and storyline for both building an attribution story and for tracking appropriate performance metrics. (Note the emphasis on engagement and relationship indicators, and behavioral indicators in recent knowledge translation research (Ottoson & Hawe, 2009). These are built in to levels 3-6 of the Canadian Cancer Society results chain hierarchy.

6. The approach applied in this case shows promise in helping to tell the Canadian Cancer Society research story in different situations and settings. In order to learn more the approach attempted here should be extended to other cases.
Appendix C: Literature Review
Discussion of Resources for Letrozole Literature Review

A brief summary of letrozole resources has been presented below for discussion with the Project Authority. The resources have been largely drawn from two parameter articles. The total number of resources retrieved numbered approximately one hundred and twenty but were distilled to seventy seven. These articles were retrieved using databases PubMed, Web of Science, BioMed Central, Cochrane, and Scopus. They have been presented by publication date order then by author within that timeframe (one year period). Where possible and based on search protocols indicating number of citations, resources were highlighted (in blue) within the table presented as “high impact” articles.

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 2009</td>
<td>Article – Follow up to Z-Fast Study</td>
<td>Zoledronic Acid Effectively Prevents Aromatase Inhibitor-Associated Bone Loss In Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: Z-FAST Study 36-Month Follow-up Results</td>
<td>BRUFSKY AM, CLINICAL BREAST CANCER 9 : 77 DOI 10.3816/CBC.2009.n.015</td>
<td>Background: Postmenopausal women with breast cancer receiving adjuvant aromatase inhibitors (Als) are at risk for accelerated bone loss and subsequent fractures. The ongoing Zometa-Femora Adjuvant Synergy Trial (Z-FAST) is evaluating the efficacy and safety of zoledronic acid in preventing such bone loss. Results: Overall, 301 patients were randomized to each group. At month 36, the absolute difference in mean LS and TH BMDs between the up-front and delayed groups was 6.7% and 5.2%, respectively (P &lt;.0001 for both). Although this study was not designed to show antifracture efficacy, the incidence of fractures was slightly higher in the delayed group (up-front, 17 [5.7%] vs. delayed, 19 [6.3%]) but not statistically significant (P=.8638). Pyrexia (27 [9%]) vs. 6 [2%], P=.0002) and bone pain (39 [13%] vs. 20 [6.7%], P = .01) were more common in up-front patients; cough (13 [4.3%] vs. 27 [9%], P=.03) was more common in delayed patients. No severe renal dysfunction or confirmed cases of osteonecrosis of the jaw were reported. Disease recurrence was reported in 9 up-front (3.0%) and 16 delayed (5.3%) patients (Kaplan-Meier analysis, P=.127), with an absolute decrease of 2.3%. Conclusion: Up-front ZA more effectively prevents Al-associated bone loss in postmenopausal women with early breast cancer than delaying therapy until substantial bone loss or fracture occurs.</td>
</tr>
<tr>
<td>2. 2009</td>
<td>Parametrie resource</td>
<td>Letrozole A Review of its Use in the Treatment of Postmenopausal Women with Hormone-Responsive Early Breast Cancer</td>
<td>Keating GM, DRUGS Volume: 69 Issue: 12 Pages: 1681-1705 Published: 2009</td>
<td>Abstract: Letrozole (Femara (R)) is a third-generation, nonsteroidal aromatase inhibitor. Adjuvant therapy with letrozole is more effective than tamoxifen in postmenopausal women with hormone-responsive early breast cancer, and extended adjuvant therapy with letrozole after the completion of adjuvant tamoxifen therapy is more effective than placebo in this patient population; letrozole is generally well tolerated. Ongoing trials will help answer outstanding questions regarding the optimal duration of letrozole therapy in early breast cancer and its efficacy compared with other third-generation aromatase inhibitors such as anastrozole. In the meantime, letrozole should be considered a valuable option in the treatment of postmenopausal women with hormone-responsive early breast cancer, both as adjuvant and extended adjuvant therapy. Pharmacological Properties Letrozole is a potent, highly selective inhibitor of aromatase; the inhibition of aromatase activity prevents the conversion of androgens to estrogens in the peripheral tissues. Reductions in whole body aromatization, aromatase activity in breast tumours, and plasma/serum levels of estrone, estradiol and estrone sulfate were seen with letrozole in postmenopausal women with breast cancer. Letrozole suppresses aromatization, plasma estrogen levels and estrogen levels within tumours to a greater extent than anastrozole, although the clinical significance of this is not clear. In general, extended adjuvant therapy with letrozole did not have deleterious effects on serum lipid levels in postmenopausal women with early breast cancer, according to the results of a substudy of the well designed, placebo-controlled MA 17 trial. Letrozole and anastrozole had generally similar effects on lipid levels. Letrozole reduced bone mineral density, according to the results of another MA 17 substudy. The results</td>
</tr>
</tbody>
</table>

null
With extended adjuvant therapy in the MA 17 trial, adverse events (all grades) that occurred in significantly more letrozole than placebo recipients included hot flushes/flashes, arthralgia, myalgia, arthritis, anorexia and alopecia. Significantly more letrozole than placebo recipients had newly diagnosed osteoporosis; however, there was no significant between-group difference in the incidence of clinical fractures. Moreover, there was no significant difference between letrozole and placebo recipients in the incidence of cardiovascular events or hypercholesterolaemia. Letrozole recipients were significantly less likely than placebo recipients to experience vaginal bleeding.

Pharmacoeconomic Considerations Markov modelling studies suggested that both adjuvant and extended adjuvant therapy with letrozole were cost effective in postmenopausal women with early breast cancer from the perspective of US, Canadian and UK healthcare systems. Incremental cost-effectiveness ratios were all below generally accepted cost-effectiveness thresholds.

### 3. 2008 Article – Letrozole zoledronic

**Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole**

**BUNDRED NJ CANCER 112 : 1001 DOI 10.1002/cnr.23259**

**BACKGROUND.** Letrozole is safe and effective in postmenopausal women with estrogen receptor-positive early breast cancer, but long-term aromatase inhibitor use may cause bone loss and increase fracture risk. This study evaluated an immediate or delayed strategy of bone protection therapy with zoledronic acid.

**METHODS.** A total of 1065 patients who were receiving adjuvant letrozole were randomized to immediate-start or delayed-start zoledronic acid (4 mg intravenously biannually for 5 years). The delayed group received zoledronic acid if lumbar spine or total hip T-score decreased below -2.0 or when a nontraumatic fracture occurred. The primary endpoint was change in lumbar spine bone mineral density (BMD) at Month 12. Secondary endpoints included changes in total hip BMD, serum bone turnover markers, and safety at Month 12.

**RESULTS.** Lumbar spine BMD increased from baseline in the immediate arm, while it decreased from baseline in delayed-arm patients. At Month 12, the differences between the groups in lumbar spine and total hip BMD were 5.7% (P < .0001; 95% confidence intervals [CI], 5.2% to 6.1%), and 3.6% (P < .0001; 95% CI, 3.3 to 4.0%), respectively. Both regimens were well tolerated with few serious adverse events. Bone pain was higher in the immediate group, as expected, because some patients experienced acute-phase reactions after zoledronic acid infusion.

**CONCLUSIONS.** At 12 months, immediate zoledronic acid therapy prevented bone loss in postmenopausal women who were receiving adjuvant letrozole.

### 4. 2008 Article – cost effectiveness

**Cost-effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in postmenopausal women with hormone-receptor positive early breast cancer from a Canadian perspective**

**DELEA TE BREAST CANCER RESEARCH AND TREATMENT 108 : 375 DOI 10.1007/s11054-007-9607-7**

**Background** In the primary core analysis of BIG 1-98, a randomized, double-blind trial comparing 5 years of initial adjuvant therapy with letrozole versus tamoxifen in postmenopausal women with hormone receptor-positive (HR+) early breast cancer, letrozole significantly improved disease-free survival by 19% and reduced the risk of breast cancer recurrence by 28% and distant recurrence by 27%.

**Methods** A Markov model was used to estimate the incremental cost per quality-adjusted life year (QALY) gained with 5 years of initial adjuvant therapy with letrozole versus tamoxifen from a Canadian healthcare system perspective. Probabilities of recurrence and side effects for tamoxifen were based on published results of BIG 1-98 and other published population-based studies. Corresponding probabilities for letrozole were calculated by multiplying probabilities for tamoxifen by estimated relative risks for letrozole versus tamoxifen from BIG 1-98. Other probabilities, costs of breast-cancer care and treatment of side effects, and health-state utilities were obtained from published studies. Costs and QALYs were estimated over the lifetime of a cohort of postmenopausal women with HR+ early breast cancer, aged 60 years at initiation of therapy, and discounted at 5% annually.

**Results** Compared with tamoxifen, letrozole yields an additional 0.368 life-years (12.453 vs. 12.086) and 0.343 QALYs (11.582 vs. 11.239). These benefits are obtained at an additional cost of $Can 8,110 ($Can 30,819 vs. $Can 22,709). Cost per QALY gained for letrozole versus tamoxifen is $Can 23,662 (95% CI $Can 15,667–$Can 52,014).

**Conclusion** In postmenopausal women with HR+ early breast cancer, initial adjuvant treatment with letrozole is cost-effective from the Canadian healthcare system perspective.

### 4. 2008 Article - Letrozole

**Late extended adjuvant treatment with letrozole**

**GOSS PE**

**Purpose** The National Cancer Institute of Canada Clinical Trials Group MA 17 trial examined the efficacy of letrozole (LET) started within 3 months of 5 years of adjuvant tamoxifen in postmenopausal hormone receptor-positive early-stage breast cancer. When the trial was unblinded, the trial was suspended. The trial was re-initiated in October 2004, with LET started within 3 months of 5 years of adjuvant tamoxifen in postmenopausal hormone receptor-positive early-stage breast cancer.
### Table 1: MA 17 Clinical Trial Case Study Findings Report

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. 2008</td>
<td>Article - NCICCTG intergroup trial MA 17</td>
<td>Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCICCTG intergroup trial MA 17</td>
<td>MUSS HB JOURNAL OF CLINICAL ONCOLOGY 26 : 1956 DOI 10.1200/JCO.2007.12.633</td>
<td>Purpose National Cancer Institute of Canada Clinical Trials Group trial MA 17 randomly assigned 5,187 postmenopausal, hormone-receptor-positive patients with early breast cancer who completed 5 years of tamoxifen to receive either letrozole or placebo. At 30 months median follow-up, letrozole significantly improved disease-free survival (DFS) in all patients and overall survival (OS) in node-positive patients. Breast cancer incidence increases with age and more than 1,300 women age 70 years or older were enrolled onto MA 17, making it ideal to explore the benefits, toxicities, and quality of life (QOL) impact of letrozole on older women. Patients and Methods In this study, 5,169 randomly assigned patients were divided into three age groups: younger than 60 years (n = 2,152), 60 to 69 years (n = 1,694), and &gt;= 70 years (n = 1,323). Log-rank test was used to compare differences in DFS, distant-disease-free survival, and OS between age and treatment groups, and Cox models were used to estimate hazard ratios and associated 95% CIs. QOL was measured using the Medical Outcomes Short Form-36 and the Menopause-Specific Quality-of-Life questionnaire. Results At 4 years, DFS demonstrated statistically significant differences favoring letrozole only in patients age younger than 60 years (hazard ratio = 0.46; P = .0004); there was no interaction between age and treatment, indicating a similar effect of letrozole among all age groups. There was no difference in toxicity or QOL at 24 months among letrozole- and placebo-treated patients age &gt;= 70 years. Conclusion Healthy patients age 70 years and older completing 5 years of tamoxifen should be considered for extended adjuvant therapy with letrozole.</td>
</tr>
<tr>
<td>6. 2008</td>
<td>Article – supplementary results from BIG 1-98</td>
<td>Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1-98 randomised trial</td>
<td>RASMUSSEN BB LANCET ONCOLOGY 9 : 23</td>
<td>Background The Breast International Group (BIG) 1-98 trial (a randomised double-blind phase III trial) has shown that letrozole significantly improves disease-free survival (DFS) compared with tamoxifen in postmenopausal women with endocrine-responsive early breast cancer. Our aim was to establish whether the benefit of letrozole versus tamoxifen differs according to the ERBB2 status of tumours. Methods The BIG 1-98 trial consists of four treatment groups that compare 5 years of monotherapy with letrozole or tamoxifen, and sequential administration of one drug for 2 years followed by the other drug for 3 years. Our study includes data from the 4922 patients randomly assigned to the two monotherapy treatment groups (letrozole or tamoxifen for 5 years; 51 months median follow-up [range &lt;1 to 90 months]): A central assessment of oestrogen receptor (ER), progesterone receptor (PgR) and ERBB2 status using paraffin-embedded primary tumour material was possible for 3650 (74%) patients. ER, PgR, and ERBB2 expression were measured by immunohistochemistry (IHC) and ERBB2-positivity was confirmed by fluorescence in-situ hybridisation (FISH). Positive staining in at least 1% of cells was considered to show presence of ER or PgR expression. Tumours were deemed ERBB2-positive if amplified by FISH, or, for few tumours with unassessable or unavailable FISH results, if they were IHC 3+. Hazard ratios (HR) estimated by Cox modelling were used to compare letrozole with tamoxifen for DFS, which was the primary endpoint, and to assess treatment-by-covariate interactions. The BIG 1-98 trial is registered on the clinical trials site of the US National Cancer institute website <a href="http://www.clinicaltrials.gov/ct/show/NCT00004205">http://www.clinicaltrials.gov/ct/show/NCT00004205</a>.</td>
</tr>
</tbody>
</table>
Findings By central assessment 7% (257 of 3550) of tumours were classified as ERBB2-positive. In 3533 patients with tumours confirmed to express ER, DFS was poorer in patients with ERBB2-positive tumours (n=239) than in those with ERBB2-negative tumours (n=3294; HR 2.09 [95% CI 1.59-2.76]; P<0.0001). There was no statistical evidence of heterogeneity in the treatment effect according to ERBB2 status of the tumour (P=0.60 for interaction), thus, letrozole improves DFS compared with tamoxifen regardless of ERBB2 status. The observed HRs were 0.62 (95% CI 0.37-1.03) for ERBB2-positive tumours and 0.72 (0.59-0.87) for ERBB2-negative tumours. Interpretation A benefit of letrozole over tamoxifen was noted, irrespective of ERBB2 status of the tumour, and, therefore, ERBB2 status does not seem to be a selection criterion for treatment with letrozole versus tamoxifen in postmenopausal women with endocrine-responsive early breast cancer.

Purpose Treatment with aromatase inhibitors decreases bone mineral density (BMD) and may increase the risk of fractures in postmenopausal women with early-stage breast cancer. The addition of zoledronic acid to adjuvant letrozole therapy may protect against bone loss. Patients and Methods Patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (LS) or total hip (TH) T score decreased to less than -2.0 or when a nontraumatic fracture occurred. The primary end point of this study was to compare the change in BMD at month 12 between the two groups. Secondary end points included change in TH BMD and changes in serum bone turnover markers at month 12. Results The upfront and delayed groups each included 301 patients. At month 12, LS BM was 4.4% higher in the upfront group than in the delayed group (95% CI, 3.7% to 5.0%; P < .0001), and TH BMD was 3.3% higher (95% CI, 2.8% to 3.8%; P < .0001). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% (P < .0001) and 8.8% (P = .0006), respectively, at month 12. Concentrations increased significantly in the delayed group by 19.5% (P = .013) and 24.3% (P < .0001), respectively. Conclusion With 1 year of follow-up, results of the primary end point of the Zoloma-Femara Adjuvant Synergy Trial (Z-FAST) indicate that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer.

Purpose Previous analyses of the Breast International Group (BIG) 1-98 four-arm study compared initial therapy with letrozole or tamoxifen including patients randomly assigned to sequential treatment whose information was censored at the time of therapy change. This presentation may thereby reflect early events, the present analysis is limited to patients randomly assigned to the continuous therapy arms and includes protocol-defined updated results. Patients and Methods Four thousand nine hundred twenty-nine of the 8,028 postmenopausal women with receptor-positive early breast cancer randomly assigned (double-blind) to the BIG 1-98 trial were assigned to 5 years of continuous adjuvant therapy with either letrozole or tamoxifen; the remainder of patients were assigned to receive the agents in sequence. Disease-free survival (DFS) was the primary end point. Results At a median follow-up time of 51 months, we observed 352 DFS events among 2,463 women receiving letrozole and 418 events among 2,459 women receiving tamoxifen. This reflected an 18% reduction in the risk of an event (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; P = .007). No predefined subsets showed differential benefit. Adverse events were similar to previous reports. Patients on tamoxifen experienced more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding. Patients on letrozole experienced more bone fractures, arthralgia, low-grade hypercholesterolemia, and cardiovascular events other than ischemia and cardiac failure. Conclusion The present updated analysis, which was limited to patients on monotherapy arms in BIG 1-98, yields results similar to those from the previous primary analysis but more directly comparable with results from other trials of continuous therapy using a single endocrine agent.

Purpose The Breast International Group (BIG) 1-98, a randomized, double-blind trial comparing 5 years of initial adjuvant therapy with letrozole versus tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer, letrozole significantly improved disease-free survival by 19% and reduced risk of breast cancer recurrence by 28% and distant recurrence by 27%. Patients and Methods: A Markov model was used to estimate the incremental cost per quality-adjusted life year (QALY) gained with 5 years of initial adjuvant therapy with letrozole versus tamoxifen from a US health care system perspective. Probabilities and costs of breast cancer recurrence and treatment-related
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Proceedings paper</td>
<td>Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and tamoxifen receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA 17</td>
<td>GOSS PE JOURNAL OF CLINICAL ONCOLOGY 25 : 2006 DOI 10.1200/JCO.2006.09.4482</td>
<td>Purpose Controversy exists regarding estrogen (ER) and progesterone (PgR) receptor expression on efficacy of adjuvant endocrine therapy. In the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, the benefit of anastrozole over tamoxifen was substantially greater in ER+/PgR- than ER+/PgR+ tumors. In BIG 1-98 (Breast International Group), the benefits of letrozole over tamoxifen were the same in ER+ tumors irrespective of PgR, MA 17 randomized postmenopausal women after 5 years of tamoxifen, to letrozole or placebo. We present outcomes according to tumor receptor status. Patients and Methods Disease-free survival (DFS) and other outcomes were assessed in subgroups by ER and PgR status using Cox's proportional hazards model, adjusting for nodal status and prior adjuvant chemotherapy. Results The DFS hazard ratio (HR) for letrozole versus placebo in ER+/PgR+ tumors (N = 3,809) was 0.49 (95% CI, 0.36 to 0.67) versus 1.21 (95% CI, 0.63 to 2.34) in ER+/PgR- tumors (n = 536). ER+/PgR- letrozole patients experienced significant benefit in distant DFS (DDFS; HR = 0.53, 95% CI, 0.35 to 0.80) and overall survival (OS; HR = 0.58, 95% CI, 0.37 to 0.90). A statistically significant difference in treatment effect between ER+/PgR+ ER-/PgR- subgroups for DFS was observed (P &lt;.02), but not for DDFS (P =.06) or OS (P =.09). Conclusion These results suggest greater benefit for letrozole in DFS DDFS and OS in patients with ER+/PgR+ tumors, implying greater activity of letrozole in tumors with a functional ER. However, because this is a subset analysis and receptors were not measured centrally we caution against, using these results for clinical decision making.</td>
</tr>
<tr>
<td>11. 2007</td>
<td>Article – BIG 1-98 trial</td>
<td>Letrozole as upfront endocrine therapy for postmenopausal women with hormone-sensitive breast cancer: BIG 1-98</td>
<td>KOEBERLE D BREAST CANCER RESEARCH AND TREATMENT 105 : 55 DOI 10.1007/s10549-007-9700-y</td>
<td>The BIG 1-98 trial is a large, randomized, independently conducted clinical trial designed to compare the efficacy of upfront letrozole versus tamoxifen monotherapy and to compare sequential or up-front use of letrozole and/or tamoxifen as an early adjuvant therapy for patients with early breast cancer. We report on the results from the primary core analysis of the BIG 1-98 trial of 8,010 patients, which compares monotherapy with letrozole versus tamoxifen. This pre-planned core analysis allowed the use of patient data from the monotherapy arms of letrozole and tamoxifen and from the sequential arms prior to the drug switch point. Patients randomized to letrozole had a 19% improved disease-free survival (hazard ratio [HR] = 0.81; P = .005), due to reduced distant metastases (HR = .73; P = .001). A 14% risk reduction of fatal events in favor of letrozole was also observed (P = .NS). The results from the monotherapy arms alone confirmed the findings from the primary core analysis. Based on the results from this trial, the aromatase inhibitor letrozole (Femara(TM)) is currently recommended as a part of standard adjuvant therapy for postmenopausal women with endocrine-responsive breast cancer and has recently been approved in the early adjuvant setting in both Europe and the United States. A subsequent analysis after additional follow-up will address the question of monotherapy versus sequential therapy.</td>
</tr>
<tr>
<td>12. 2007</td>
<td>Article - review</td>
<td>A decade of letrozole: FACE</td>
<td>OSHAUGHNESSY J BREAST CANCER RESEARCH AND TREATMENT 105 : 67 DOI 10.1007/s10549-007-</td>
<td>Third-generation nonsteroidal aromatase inhibitors (AIs), letrozole and anastrozole, are superior to tamoxifen as initial therapy for early breast cancer but have not been directly compared in a head-to-head adjuvant trial. Cumulative evidence suggests that AIs are not equivalent in terms of potency of estrogen suppression and that there may be differences in clinical efficacy. Thus, with no data from head-to-head comparisons of the AIs as adjuvant therapy yet available, the question of whether there are efficacy differences between the AIs remains. To help answer this question, the Femara versus Anastrozole Clinical Evaluation (FACE) is a phase IIIb open-label, randomized, multicenter trial designed to test whether letrozole or anastrozole has superior efficacy as adjuvant treatment of postmenopausal women with hormone receptor (HR)- and lymph node-positive breast cancer. Eligible patients [target accrual, N = 4,000] are randomized to receive either letrozole 2.5 mg or anastrozole 1 mg</td>
</tr>
</tbody>
</table>
daily for up to 5 years. The primary objective is to compare disease-free survival at 5 years. Secondary end points include safety, overall survival, time to distant metastases, and time to contralateral breast cancer. The FACE trial will determine whether or not letrozole offers a greater clinical benefit to postmenopausal women with HR+ early breast cancer at increased risk of early recurrence compared with anastrozole.

Purpose To evaluate locally versus centrally assessed estrogen (ER) and progesterone (PgR) receptor status and the impact of PgR on letrozole adjuvant therapy compared with tamoxifen in postmenopausal women with early breast cancer. Patients and Methods Breast International Group (BIG) 1-98 randomly assigned 8,010 patients to four arms comparing letrozole and tamoxifen with sequences of each agent. The Central Pathology Office received material for 6,549 patients (82%), of which 79% were assessable (6,291 patients). Prognostic and predictive value of both local and central hormone receptor expression on disease-free survival (DFS) were evaluated among 3,650 assessable patients assigned to the monotherapy arms. Prognostic value and the treatment effect were estimated for centrally assessed ER and PgR expression levels using the Subpopulation Treatment Effect Pattern Plot.

Results Central review confirmed 97% of tumors as hormone receptor-positive (ER and/or PgR > 10%). Of 105 tumors locally ER-negative, 73 were found to have more than 10% positive cells, and eight had 1% to 9%. Of 6,100 tumors locally ER-positive, 66 were found to have no staining, and 54 had only 1% to 9%. Discordance was more marked for PgR than ER. Patients with tumors reclassified centrally as ER-negative, or as hormone receptor-negative, had poor DFS. Centrally assessed ER and PgR showed prognostic value. Among patients with centrally assessed ER-expressing tumors, letrozole showed better DFS than tamoxifen, irrespective of PgR expression level.

Conclusion Central review changed the assessment of receptor status in a substantial proportion of patients, and should be performed whenever possible in similar trials. PgR expression did not affect the relative efficacy of letrozole over tamoxifen.

Conclusions: For postmenopausal women with early breast cancer who have completed 5 years of adjuvant tamoxifen, the cost-effectiveness of extended adjuvant letrozole is within the range of other generally accepted medical interventions in the United States.

Conclusion: For postmenopausal women with early breast cancer who have completed 5 years of adjuvant tamoxifen, the cost-effectiveness of extended adjuvant letrozole is within the range of other generally accepted medical interventions in the United States.
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. 2006</td>
<td>Article – pharmacoeconomic review</td>
<td>Letrozole - A pharmacoeconomic review of its use in postmenopausal women with breast cancer</td>
<td>DUNN C PHARMACOECONOMIC S 24 : 495</td>
<td>Letrozole (Femara(R)), an aromatase inhibitor that blocks estrogen synthesis by inhibiting the final step of the estrogen biosynthetic pathway, is approved for use in a wide range of breast cancer settings. Randomised clinical trials in postmenopausal women with hormone-responsive early-stage breast cancer have demonstrated that, as adjuvant therapy, letrozole has greater efficacy than tamoxifen. It is also more effective than placebo as extended adjuvant therapy after completion of tamoxifen therapy in these patients. In women with hormone-responsive advanced breast cancer, letrozole is superior to tamoxifen in prolonging the time to disease progression and time to treatment failure in a first-line setting, and is at least as effective as anastrozole and more effective than megestrol for some endpoints (in one of two trials) in a second-line setting. Letrozole is generally well tolerated, and in a health-related quality-of-life analysis from a large clinical trial, patient well-being with letrozole as extended adjuvant therapy did not differ from that with placebo. Modelled analyses from the UK and the US suggest that, in postmenopausal women with hormone-receptor-positive early-stage breast cancer, letrozole is likely to be a cost-effective alternative to tamoxifen as adjuvant therapy; moreover, using letrozole as extended adjuvant therapy after tamoxifen, rather than no further treatment, is also a cost-effective treatment strategy. Sensitivity analyses have shown these results to be robust. In terms of direct healthcare costs, pharmacoeconomic models suggest that letrozole is a cost-effective alternative to tamoxifen as first-line therapy in postmenopausal women with hormone-responsive advanced breast cancer from the perspectives of the UK NHS, the Canadian and Italian public healthcare systems and the Japanese national health insurance system. Incremental costs per QALY or progression-free year gained over tamoxifen were well within the recommended limits for acceptability of new agents that are more effective and more expensive than existing therapies in the UK, Japan and Canada. Modelled analyses from the UK and Canada have also suggested that letrozole is cost effective as second-line therapy for advanced breast cancer in postmenopausal women who have disease progression following anti-estrogen therapy. In conclusion, letrozole is an effective and well tolerated treatment for postmenopausal women with early-stage or advanced hormone-responsive breast cancer. Pharmacoeconomic analyses from UK and North American perspectives support the use of letrozole in hormone-responsive early-stage breast cancer in both the adjuvant and extended adjuvant settings. In addition, other modelled analyses conducted in a variety of healthcare systems across different countries consistently suggest that letrozole is cost effective in advanced treatment settings.</td>
</tr>
<tr>
<td>17. 2006</td>
<td>Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: A companion study to</td>
<td>PEREZ EA JOURNAL OF CLINICAL ONCOLOGY 24 : 3629 DOI 10.1200/JCO.2005.05.488 2</td>
<td>Purpose Aromatase inhibition depletes estrogen levels and may be associated with accelerated bone resorption. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) study MA 17B evaluated bone turnover markers and bone mineral density (BMD) in postmenopausal women randomly assigned to MA 17, a placebo-controlled trial of letrozole after standard adjuvant tamoxifen. Patients and Methods Eligible women had a baseline BMD T score of at least 2.0 in either the hip or L2-L4 spine; all received calcium 500 mg and vitamin D 400 U daily. Percentage change in BMD (L2-L4 spine and hip) at 12 and 24 months, rate of osteoporosis, and change in markers of bone formation (serum bone alkaline phosphatase) and resorption (serum C-telopeptide and urine N-telopeptide) at 6, 12, and 24 months were compared.</td>
<td>Modelled analyses from the UK and the US suggest that, in postmenopausal women with hormone-receptor-positive early-stage breast cancer, letrozole is likely to be a cost-effective alternative to tamoxifen as adjuvant therapy; moreover, using letrozole as extended adjuvant therapy after tamoxifen, rather than no further treatment, is also a cost-effective treatment strategy. Sensitivity analyses have shown these results to be robust. In terms of direct healthcare costs, pharmacoeconomic models suggest that letrozole is a cost-effective alternative to tamoxifen as first-line therapy in postmenopausal women with hormone-responsive advanced breast cancer from the perspectives of the UK NHS, the Canadian and Italian public healthcare systems and the Japanese national health insurance system. Incremental costs per QALY or progression-free year gained over tamoxifen were well within the recommended limits for acceptability of new agents that are more effective and more expensive than existing therapies in the UK, Japan and Canada. Modelled analyses from the UK and Canada have also suggested that letrozole is cost effective as second-line therapy for advanced breast cancer in postmenopausal women who have disease progression following anti-estrogen therapy. In conclusion, letrozole is an effective and well tolerated treatment for postmenopausal women with early-stage or advanced hormone-responsive breast cancer. Pharmacoeconomic analyses from UK and North American perspectives support the use of letrozole in hormone-responsive early-stage breast cancer in both the adjuvant and extended adjuvant settings. In addition, other modelled analyses conducted in a variety of healthcare systems across different countries consistently suggest that letrozole is cost effective in advanced treatment settings.</td>
</tr>
</tbody>
</table>
Background. Most recurrences in women with breast cancer receiving 5 years of adjuvant tamoxifen occur after 5 years. The MA 17 trial, which was designed to determine whether extended adjuvant therapy with the aromatase inhibitor letrozole after tamoxifen reduces the risk of such late recurrences, was stopped early after an interim analysis showed that letrozole improved disease-free survival. This report presents updated findings from the trial. Methods: Postmenopausal women completing 5 years of tamoxifen treatment were randomly assigned to a planned 5 years of letrozole (n = 2593) or placebo (n = 2594). The primary endpoint was disease-free survival (DFS); secondary endpoints included distant disease-free survival, overall survival, incidence of contralateral tumors, and toxic effects. Survival was examined using Kaplan-Meier analysis and log-rank tests. Planned subgroup analyses included those by axillary lymph node status. All statistical tests were two-sided. Results: After a median follow-up of 30 months (range = 1.5-61.4 months), women in the letrozole arm had statistically significantly better DFS and distant DFS compared to those receiving placebo, but the incidences of bone fractures and cardiovascular events were the same. Conclusion: Letrozole after tamoxifen is well-tolerated and improves both disease-free and distant disease-free survival but not overall survival, except in node-positive patients.

Back ground. Most recurrences in women with breast cancer receiving 5 years of adjuvant tamoxifen occur after 5 years. The MA 17 trial, which was designed to determine whether extended adjuvant therapy with the aromatase inhibitor letrozole after tamoxifen reduces the risk of such late recurrences, was stopped early after an interim analysis showed that letrozole improved disease-free survival. This report presents updated findings from the trial. Methods: Postmenopausal women completing 5 years of tamoxifen treatment were randomly assigned to a planned 5 years of letrozole (n = 2593) or placebo (n = 2594). The primary endpoint was disease-free survival (DFS); secondary endpoints included distant disease-free survival, overall survival, incidence of contralateral tumors, and toxic effects. Survival was examined using Kaplan-Meier analysis and log-rank tests. Planned subgroup analyses included those by axillary lymph node status. All statistical tests were two-sided. Results: After a median follow-up of 30 months (range = 1.5-61.4 months), women in the letrozole arm had statistically significantly better DFS and distant DFS compared to those receiving placebo, but the incidences of bone fractures and cardiovascular events were the same. Conclusion: Letrozole after tamoxifen is well-tolerated and improves both disease-free and distant disease-free survival but not overall survival, except in node-positive patients.

The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen, but recurrences and side-effects restrict its usefulness. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localised breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged...
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. 2005</td>
<td>Article – BIG 1-98 trial</td>
<td>A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer</td>
<td>THURLIMANN B NEW ENGLAND JOURNAL OF MEDICINE 353 : 2747</td>
<td>The aromatase inhibitor letrozole is a more effective treatment for metastatic breast cancer and more effective in the neoadjuvant setting than tamoxifen. We compared letrozole with tamoxifen as adjuvant treatment for steroid-hormone-receptor-positive breast cancer in postmenopausal women. Methods The Breast International Group (BIG) 1-98 study is a randomized, phase 3, double-blind trial that compared five years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor-positive breast cancer: letrozole, tamoxifen, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. This analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment groups were included up to the time that treatments were switched. Results A total of 8010 women with data that could be assessed were enrolled, 4003 in the letrozole group and 4007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with five-year disease-free survival estimates of 84.0 percent and 81.4 percent, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (hazard ratio, 0.81; 95 percent confidence interval, 0.70 to 0.93; P = 0.003), especially the risk of distant recurrence (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; P &lt; 0.001). Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolemia. Conclusions In postmenopausal women with hormone-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites.</td>
</tr>
<tr>
<td>22. 2005</td>
<td>Article - MA 17L substudy</td>
<td>The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA 17L)</td>
<td>WASAN KM ANNALS OF ONCOLOGY 16 : 707 DOI 10.1093/annonc/mdl158</td>
<td>The purpose of this study was to evaluate changes in serum lipid parameters (cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and lipoprotein(a) [Lp(a)]), in postmenopausal women receiving letrozole or placebo after adjuvant tamoxifen for early stage breast cancer (NCIC CTG MA 17L). Patients and methods: MA 17L is a substudy of MA 17, a randomized, double-blind, placebo-controlled trial of letrozole 2.5 mg taken daily for 5 years in postmenopausal women with primary breast cancer completing similar to 5 years of prior adjuvant tamoxifen. Patients consenting to participate in this companion study had blood drawn and lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, Lp(a), triglycerides) evaluated at baseline, 6 months, 12 months, 16 years and yearly thereafter until completion of protocol therapy. It was required that women be non-hyperlipidemic and not taking lipid-lowering drugs at time of entry on this trial. Results: Three hundred and forty seven women were enrolled in the study. The letrozole and the placebo groups demonstrated marginally significant differences in the percentage change from baseline in HDL cholesterol at 6 months (P = 0.048), in LDL cholesterol at 12 months (P = 0.033) and triglycerides at 24 months (P = 0.036). All comparisons of lipid parameters at other time points were not significantly different between the two treatment groups. No statistically significant differences in the number of patients exceeding the thresholds defined for the lipid parameters were found between the two treatment groups. Conclusions: The MA 17 trial demonstrated a significant improvement in disease-free survival with the use of letrozole as extended adjuvant therapy post tamoxifen. Results from this study suggests that letrozole does not significantly alter serum cholesterol, HDL cholesterol, LDL cholesterol, triglycerides or Lp(a) in non-hyperlipidemic postmenopausal women with primary breast cancer treated up to 36 months following at least 5 years of adjuvant tamoxifen therapy. These findings further support the tolerability of extended adjuvant letrozole in postmenopausal</td>
</tr>
<tr>
<td>Year Published</td>
<td>Legend Guide</td>
<td>Resource Title</td>
<td>Primary Author and Journal Reference</td>
<td>Resource Abstract</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>23. 2005</td>
<td>Article – MA 17 QOL substudy</td>
<td>Assessment of quality of life in MA 17: A randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women</td>
<td>WHELAN TJ JOURNAL OF CLINICAL ONCOLOGY 23 : 6901 DOI 10.1200/JCO.2005.11.181</td>
<td>To evaluate the impact of letrozole compared with placebo after adjuvant tamoxifen on quality of life (QOL) in the MA 17 trial. Methods Patients completed the Short Form 36-item Health Survey (SF-36) and the Menopause Specific Quality of Life Questionnaire (MENQOL) at baseline, 6 months, and annually. Mean change scores from baseline were compared between groups for summary measures and domains. A response analysis compared the proportion of patients who demonstrated an important change in QOL. Results Of 5,187 randomly assigned women in the trial, 3,612 (69.9%) participated in the QOL substudy: 1,799 were allocated to placebo and 1,813 were allocated to letrozole. No differences were seen between groups in mean change scores from baseline for the SF-36 physical and mental component summary scores at 6, 12, 24, and 36 months. Small (p &lt; 0.2 standard deviations) but statistically significant differences in mean change scores from baseline were seen for the SF-36 domains of physical functioning (12 months), bodily pain (6 months) and vitality (6 and 12 months), and the MENQOL vasomotor (6, 12, and 24 months), and sexual domains (12 and 24 months). On the response analysis, a significant difference was seen between groups for the bodily pain domain (percentage of patients reporting a worsening of QOL, 47% placebo v 51% letrozole; P = 0.009) and the vasomotor domain (22% placebo v 29% letrozole; P = 0.001). Conclusion Letrozole did not have an adverse impact on overall QOL. Small effects were seen in some domains consistent with a minority of patients experiencing changes in QOL compatible with a reduction in estrogen synthesis.</td>
</tr>
<tr>
<td>24. 2005</td>
<td>Clinical update</td>
<td>American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004</td>
<td>WINER EP JOURNAL OF CLINICAL ONCOLOGY 23 : 619 DOI 10.1002/JCO.2005.09.121</td>
<td>Purpose To update the 2003 American Society of Clinical Oncology technology assessment on adjuvant use of aromatase inhibitors. Recommendations Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contra indications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy, consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, or 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor-negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized. Conclusion The Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.</td>
</tr>
<tr>
<td>25. 2004</td>
<td>Article - review</td>
<td>Letrozole - A review of its use in postmenopausal women with breast cancer</td>
<td>SIMPSON D DRUGS 64 : 1213</td>
<td>Letrozole (Femara®), a nonsteroidal, third-generation aromatase inhibitor administered orally once daily, has shown efficacy in the treatment of postmenopausal women with early-stage or advanced, hormone-sensitive breast cancer. In early-stage disease, extending adjuvant endocrine therapy with letrozole (beyond the standard 5-year period of tamoxifen) improved disease-free survival: compared with placebo there was a 43% relative reduction in disease recurrences or new contralateral breast tumours at a median follow-up of 2.4 years. The results of 4 months' neoadjuvant treatment with letrozole or tamoxifen in postmenopausal women with untreated primary disease favour letrozole. In advanced breast cancer, letrozole was superior to tamoxifen as first-line treatment; time to disease progression was significantly longer (9.4 vs 6.0 months, p &lt; 0.0001) and objective response rate was significantly greater with letrozole, but median overall survival was similar between groups. For second-line therapy of advanced breast cancer that had progressed on antiestrogen therapy, letrozole showed efficacy equivalent to that of anastrozole and similar to or better than that of megesterol acetate. Letrozole is generally well tolerated and has a similar tolerability profile to tamoxifen; the most common treatment-related adverse events were</td>
</tr>
<tr>
<td>Year Published</td>
<td>Legend Guide</td>
<td>Resource Title</td>
<td>Primary Author and Journal Reference</td>
<td>Resource Abstract</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status</td>
<td>ELLIS MJ CANCER RESEARCH 63: 6623</td>
<td>Background: The biological basis for the superior efficacy of neoadjuvant letrozole versus tamoxifen for postmenopausal women with estrogen receptor (ER)-positive locally advanced breast cancer was investigated by analyzing tumor proliferation and expression of estrogen-regulated genes before and after the initiation of therapy. Methods: Tumor samples were obtained at baseline and at the end of treatment from 185 patients participating in a double-blind randomized Phase III study of neoadjuvant endocrine therapy. These paired specimens were simultaneously analyzed for Ki67, ER, progesterone receptor (PgR), trefoil factor 1 (PS2), HER1 (epidermal growth factor receptor), and HER2 (ErbB2 or neu) by semiquantitative immunohistochemistry. Results: The treatment-induced reduction in geometric mean Ki67 was significantly greater with letrozole (87%) than tamoxifen (75%; analysis of covariance P = 0.0009). Differences in the average Ki67 reduction were particularly marked for ER-positive tumors that overexpressed HER1 and/or HER2 (88 versus 45%, respectively; P = 0.0018). Twenty-three of 92 tumors (25%) on tamoxifen and 14 of 93 on letrozole (15%) showed a paradoxical increase in Ki67 with treatment, and the majority of these cases was HER1/2 negative. Letrozole, but not tamoxifen, significantly reduced expression of the estrogen-regulated proteins PgR and trefoil factor 1, regardless of HER1/2 status (P &lt; 0.0001). ER down-regulation occurred with both agents, although levels decreased more with tamoxifen (P &lt; 0.0001). Conclusion: Letrozole inhibits tumor proliferation to a greater extent than tamoxifen. The molecular basis for this advantage appears complex but includes possible tamoxifen agonist effects on the cell cycle in both HER1/2+ and HER1/2- tumors. A pattern of continued proliferation despite appropriate down-regulation of PgR expression with estrogen deprivation or tamoxifen was also documented. This observation suggests the estrogenic regulation of proliferation and PgR expression may be dissociated in endocrine therapy resistant cells.</td>
</tr>
</tbody>
</table>
| 2003           |              | A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer | Goss, PE NEW ENGLAND JOURNAL OF MEDICINE, 349 (19): 1793-1802 | In hormone-dependent breast cancer, five years of postoperative tamoxifen therapy -- but not tamoxifen therapy of longer duration -- prolongs disease-free and overall survival. The aromatase inhibitor letrozole, by suppressing estrogen production, might improve the outcome after the discontinuation of tamoxifen therapy. METHODS A double-blind, placebo-controlled trial to test the effectiveness of five years of letrozole therapy in postmenopausal women with breast cancer who have completed five years of tamoxifen therapy. The primary end point was disease-free survival. RESULTS A total of 5187 women were enrolled (median follow-up, 2.4 years). At the first interim analysis, there were 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast -- 75 in the letrozole group and 132 in the placebo group -- with estimated four-year disease-free survival rates of 93 percent and 87 percent, respectively, in the two groups (P < 0.001 for the comparison of disease-free survival). A total of 42 women in the placebo group and 31 women in the letrozole group died (P < 0.25 for the comparison of overall survival). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal }
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. 2003</td>
<td>Article – clinical update</td>
<td>American society of clinical oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer</td>
<td>HILLNER BE JOURNAL OF CLINICAL ONCOLOGY 21 : 4042 DOI 10.1200/JCO.2003.08.017</td>
<td>bleeding was less frequent. There were new diagnoses of osteoporosis in 5.8 percent of the women in the letrozole group and 4.5 percent of the women in the placebo group (P=0.07); the rates of fracture were similar. After the first interim analysis, the independent data and safety monitoring committee recommended termination of the trial and prompt communication of the results to the participants. CONCLUSIONS: As compared with placebo, letrozole therapy after the completion of standard tamoxifen treatment significantly improves disease-free survival.</td>
</tr>
<tr>
<td>29. 2003</td>
<td>Article – letrozole comparison</td>
<td>Signaling pathways of apoptosis activated by aromatase inhibitors and antiestrogens</td>
<td>THIANTANAWAT A CANCER RESEARCH 63 : 8037</td>
<td>Aromatase inhibitors have recently been reported to be more effective than the antiestrogen tamoxifen (Tam) in treating breast cancer. Here, we studied the mechanisms and signaling pathways of cell growth, cell cycle progression, and apoptosis induced by three aromatase inhibitors: letrozole (Let), anastrozole, and 4-hydroxyandrostenedione in comparison with estrogen withdrawal (EM) and antiestrogens Tam and faslodex. Estrogen-dependent human breast cancer cells stably transfected with aromatase (MCF-7Ca) were used. All treatments induced growth suppression and cell cycle arrest at the G0-G1 phase that was associated with up-regulation of p53 and p21 protein and mRNA levels and down-regulation of cyclin D1 and c-myc mRNA. The apoptotic index was increased 4.7 fold, Bcl-2 protein expression decreased, Bax increased, and caspase-9, caspase-6, and caspase-7 were activated but not caspase-3 and caspase-8. Let and E2W caused regression of tumors of MCF-7Ca cells grown in nude mice and increased the number of cells undergoing apoptosis. In contrast, Tam and faslodex did not induce tumor regression and a lower number of apoptotic cells was detected. Cleavage of poly(ADP-ribose) polymerase was detected. Treatment with Let, Tam, or E2W resulted in a dose- and time-dependent increase in active caspase-7 and up-regulation of p53 and p21 protein. Although the mechanisms involved appeared to be similar for antiestrogens and aromatase inhibitors, the most significant effects occurred with Let, which were significantly greater than with E2W and consistent with marked effects of Let on tumor and cell growth.</td>
</tr>
<tr>
<td>30. 2003</td>
<td>Article – clinical update</td>
<td>American society of clinical oncology technology assessment working group update: Use of aromatase inhibitors in the adjuvant</td>
<td>WINER EP JOURNAL OF CLINICAL ONCOLOGY 21 : 2597 DOI</td>
<td>In December 2001, the initial results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study were presented at the San Antonio Breast Cancer Symposium. At the time of the report, with a median reported follow-up of 33 months, there was a statistically significant improvement in disease-free survival for postmenopausal women who received adjuvant mono-therapy with anastrozole in comparison with those who received monotherapy with tamoxifen. The American Society of Clinical Oncology (ASCO) convened a Technology Assessment Working Group to review the available data and to develop a series of recommendations regarding the optimal use of aromatase inhibitors as adjuvant breast cancer therapy. Since the initial presentation of the ATAC results in 2001, the results of the study have been peer reviewed and</td>
</tr>
<tr>
<td>Year Published</td>
<td>Legend Guide</td>
<td>Resource Title</td>
<td>Primary Author and Journal Reference</td>
<td>Resource Abstract</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>----------------</td>
<td>--------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>31. 2002</td>
<td>Article – ATAC trial</td>
<td>Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial</td>
<td>BAUM M LANCET 359 : 2131</td>
<td>Background In the adjuvant setting, tamoxifen is the established treatment for postmenopausal women with hormone-sensitive breast cancer. However, it is associated with several side-effects including endometrial cancer and thromboembolic disorders. We aimed to compare the safety and efficacy outcomes of tamoxifen with those of anastrozole alone and the combination of anastrozole plus tamoxifen for 5 years. Methods Participants were postmenopausal breast cancer patients who had completed primary therapy and were eligible to receive adjuvant hormonal therapy. The primary endpoints were disease-free survival and occurrence of adverse events. Analysis for efficacy was by intention to treat. Findings 9386 patients were recruited, of whom 3125 were randomly assigned anastrozole, 3116 tamoxifen, and 3125 combination. Median follow-up was 33.3 months. 7839 (84%) patients were known to be hormone-receptor-positive. Disease-free survival at 3 years was 89.4% on anastrozole and 87.4% on tamoxifen (hazard ratio 0.83 [95% CI 0.71-0.96], p=0.013). Results with the combination were not significantly different from those with tamoxifen alone (87.2%, 1.02 [0.89-1.18], p=0.8). The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone-receptor-positive patients, but not the receptor-negative patients. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio 0.42 [0.22-0.79], p=0.007). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p=0.02), vaginal bleeding and discharge (p=0.0001 for both), cerebrovascular events (p=0.0006), venous thromboembolic events (p=0.0066), and hot flushes (p=0.0001). Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures (p=0.0001 for both). Interpretation Anastrozole is an effective and well-tolerated endocrine option for the treatment of postmenopausal patients with hormone-sensitive early breast cancer. Longer follow-up is required before a final benefit:risk assessment can be made.</td>
</tr>
<tr>
<td>32. 2002</td>
<td>Proceedings</td>
<td>Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study</td>
<td>GEISLER J JOURNAL OF CLINICAL ONCOLOGY 20 : 751</td>
<td>Purpose: To compare the effects of the two novel, potent, nonsteroidal aromatase inhibitors anastrozole and letrozole on total-body aromatization and plasma estrogen levels. Patients and Methods: Twelve postmenopausal women with estrogen receptor-positive, metastatic breast cancer were treated with anastrozole 1 mg orally (PO) and letrozole 2.5 mg PO once daily, each given for a time interval of 6 weeks in a randomized sequence. Total-body aromatization was determined before treatment and at the end of each treatment period using a dual-label isotopic technique involving isolation of the metabolites with high-performance liquid chromatography. Plasma levels of estrone (E1), estradiol (E2), and estrone sulfate (ES) were determined in samples obtained before each injection using highly sensitive radioimmunoassays. Results: Pretreatment aromatase levels ranged from 1.66% to 4.27%. On-treatment levels of aromatase were detectable in 11 of 12 patients during treatment with anastrozole (mean percentage inhibition in the whole group, 97.3%) but in none of the 12 patients during treatment with letrozole (&gt; 99.1% suppression in all patients; Wilcoxon, P = .0022, comparing the two drug regimens). Treatment with anastrozole suppressed plasma levels of E1, E2, and ES by a mean of 81.0%, 84.9%, and 93.5%, respectively, whereas treatment with letrozole caused a corresponding decrease of 84.3%, 87.8%, and 98.0%, respectively. The suppression of E, ES and E2 was found to be significantly better during treatment with letrozole compared with anastrozole (P = .019 and .0037, respectively). Conclusion: This study revealed letrozole (2.5 mg once daily) to be a more potent suppressor of total-body aromatization and plasma estrogen levels compared with anastrozole (1 mg once daily) in postmenopausal women with metastatic breast cancer.</td>
</tr>
<tr>
<td>33. 2002</td>
<td>Article – pilot study</td>
<td>Effects of the aromatase inhibitors anastrozole and tamoxifen on normal breast epithelial cell proliferation and metabolic processes</td>
<td>HARPER-WYNNE C CANCER EPIDEMIOLOGY</td>
<td>The aromatase enzyme converts androgens to estrogens and is the therapeutic target for aromatase inhibitors in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. Third-generation inhibitors such as letrozole are being considered as potential prophylactic agents for breast cancer. The rationale for their preventive application would be aided by knowledge of their effects on the normal breast and on other estrogen-dependent processes such as bone and lipid metabolism. Thirty-two women without active breast disease were recruited to 3-</td>
</tr>
<tr>
<td>Year Published</td>
<td>Legend Guide</td>
<td>Resource Title</td>
<td>Primary Author and Journal Reference</td>
<td>Resource Abstract</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>34. 2002</td>
<td>Article – letrozole bone formation</td>
<td>Role of low levels of endogenous estrogen in regulating bone resorption in late postmenopausal women</td>
<td>HESHMATI HM JOURNAL OF BONE AND MINERAL RESEARCH 17 : 172</td>
<td>Although median levels of bone turnover are increased in postmenopausal women, it is unclear whether the low circulating levels of endogenous estrogen exert a regulatory role on these levels. This issue was evaluated by assessing the effect of a blockade of estrogen synthesis on bone turnover. Estrone and estradiol levels were measured in normal women (age 50–69 years) randomly assigned to groups receiving the potent aromatase inhibitor letrozole or placebo for 6 months. Letrozole treatment reduced serum estrone (E1) and estradiol (E2) to near undetectable levels (p &lt; 0.0001). This treatment did not affect bone formation markers but, as compared with the placebo group, increased bone resorption markers (urine 24-h pyridinoline [PYD] by 13.3% [p &lt; 0.05] and 24-h urine deoxypyridinoline [DPD] by 14.2% [p = 0.05]) and decreased serum parathyroid hormone (PTH) by 22% (p = 0.002). These data indicate that in late postmenopausal women even the low serum estrogen levels present exert a restraining effect on bone turnover and support the concept that variations in these low levels may contribute to differences in their rate of bone loss.</td>
</tr>
<tr>
<td>35. 2002</td>
<td>Article – second line antiestrogens</td>
<td>The effect of second-line antiestrogen therapy on breast tumor growth after first-line treatment with the aromatase inhibitor letrozole: Long-term studies using the intratumoral aromatase postmenopausal breast cancer model</td>
<td>LONG BJ CLINICAL CANCER RESEARCH 8 : 2378</td>
<td>Purpose: The aromatase inhibitors letrozole and anastrozole have been approved recently as first-line treatment options for hormone-dependent advanced breast cancer. Although it is established that a proportion of patients who relapse on first-line tamoxifen therapy show additional responses to aromatase inhibitors, it has not been determined whether tumors that acquire resistance to aromatase inhibitors in the first line remain sensitive to second-line therapy with antiestrogens. The aim of this study was to determine whether aromatase-transfected and hormone-dependent MCF-7Ca human breast cancer cells remain sensitive to antiestrogens after: (a) long-term growth in steroid-depleted medium in vitro; and (b) long-term treatment with the aromatase inhibitor letrozole in vivo. Methods: In the first approach, a variant of the MCF-7Ca human breast cancer cell line was selected that had acquired the ability to grow in estrogen-depleted medium after 6-8 months of culture. Steroid-deprived UMB-1Ca cells were analyzed for aromatase activity levels, hormone receptor levels, and sensitivity to estrogens and antiestrogens in vitro and in vivo. In the second approach, established MCF-7Ca breast tumor xenografts were treated with letrozole 10 μg/day for 12 weeks followed by 100 μg/day for 25 weeks until tumors acquired the ability to proliferate in the presence of the drug. Long-term letrozole-treated tumors were then transplanted into new mice, and the effects of antiestrogens and aromatase inhibitors on tumor growth were determined. Results: Steroid-deprived UMB-1Ca breast cancer cells continued to express aromatase activity at levels comparable with the parental cell line. However, compared with MCF-7Ca cells, UMB-1Ca cells expressed elevated levels of functionally active estrogen receptor. The growth of UMB-1Ca cells in vitro was inhibited by the antiestrogens tamoxifen and faslodex and tumor growth in vivo was inhibited by tamoxifen. In the second approach, the time for MCF-7Ca tumor xenografts to approximately double in volume after being treated sequentially with the increasing doses of letrozole was thirty-seven weeks. Long-term letrozole-treated tumors continued to express functionally active aromatase. When transplanted into new mice, growth of the long-term letrozole-treated tumors was slowed by tamoxifen and inhibited more effectively by faslodex. Tumor growth was refractory to the aromatase inhibitors anastrozole and formestane but, surprisingly, showed sensitivity to letrozole. Conclusions: Steroid-deprived UMB-1Ca human breast cancer cells selected in vitro and long-term letrozole-treated MCF-7Ca breast tumor xenografts remain sensitive to second-line therapy with antiestrogens and, in particular, to faslodex. This finding is associated with increased expression of functionally active estrogen receptor after steroid-deprivation of MCF-7Ca human breast cancer cells in vitro.</td>
</tr>
<tr>
<td>36. 2002</td>
<td>Article – second line antiestrogens</td>
<td>The effect of second-line antiestrogen therapy on breast tumor growth after</td>
<td>Long BJ CLINICAL CANCER</td>
<td>Purpose: The aromatase inhibitors letrozole and anastrozole have been approved recently as first-line treatment options for hormone-dependent advanced breast cancer. Although it is established that a proportion of patients who relapse on first-line tamoxifen therapy show additional responses to aromatase inhibitors, it has not been determined whether tumors that acquire resistance to aromatase</td>
</tr>
</tbody>
</table>
Inhibitors in the first line remain sensitive to second-line therapy with antiestrogens. The aim of this study was to determine whether aromatase-transfected and hormone-dependent MCF-7Ca human breast cancer cells remain sensitive to antiestrogens after: (a) long-term growth in steroid-depleted medium in vitro; and (b) long-term treatment with the aromatase inhibitor letrozole in vivo.

Methods: In the first approach, a variant of the MCF-7Ca human breast cancer cell line was selected that had acquired the ability to grow in estrogen-depleted medium after 6-8 months of culture. Steroid-deprived UMB-1Ca cells were analyzed for aromatase activity levels, hormone receptor levels, and sensitivity to estrogens and antiestrogens in vitro and in vivo.

Results: Steroid-deprived UMB-1Ca breast cancer cells continued to express aromatase activity at levels comparable with the parental cell line. However, compared with MCF-7Ca cells, UMB-1Ca cells expressed equal levels of functionally active estrogen receptor. The growth of UMB-1Ca cells in vitro was inhibited by the antiestrogens tamoxifen and faslodex and tumor growth in vivo was inhibited by tamoxifen. In the second approach, long-term letrozole-treated MCF-7Ca tumor xenografts to approximately double in volume after being treated sequentially with the increasing doses of letrozole was thirty-seven weeks. Long-term letrozole-treated tumors continued to express functionally active aromatase. When transplanted into new mice, growth of the long-term letrozole-treated tumors was slowed by tamoxifen and inhibited more effectively by faslodex. Tumor growth was refractory to the aromatase inhibitors anastrozole and formestane but, surprisingly, showed sensitivity to letrozole.

Conclusions: Steroid-deprived UMB-1Ca human breast cancer cells selected in vitro and long-term letrozole-treated MCF-7Ca breast tumor xenografts remain sensitive to second-line therapy with antiestrogens and, in particular, to faslodex. This finding is associated with increased expression of functionally active estrogen receptor after steroid-deprivation of MCF-7Ca human breast cancer cells in vitro.

Objective: To conduct an evidence-based technology assessment to determine whether the routine use of anastrozole or any of the aromatase inhibitors in the adjuvant breast cancer setting is appropriate for broad-based conventional use in clinical practice.

Potential Interventions: Anastrozole, letrozole, and exemestane.

Outcomes: Outcomes of interest include breast cancer incidence, breast cancer-specific survival, overall survival, and net health benefit.

Evidence: A comprehensive, formal literature review was conducted for relevant topics and is detailed in the text. Testimony was collected from invited experts and interested parties. The American Society of Clinical Oncology (ASCO)-prescribed technology assessment procedure was followed.

Benefits/Harms: The ASCO panel recognizes that a woman and her physician's decision regarding adjuvant hormonal therapy is complex and will depend on the importance and weight attributed to information regarding both cancer and non-cancer-related risks and benefits.

Conclusion: The panel was influenced by the compelling, extensive, and long-term data available on tamoxifen. Overall, the panel considers the results of the Arimidex (anastrozole) or Tamoxifen Alone or in Combination (ATAC) trial and the extensive supporting data to be very promising but insufficient to change the standard practice at this time (May 2002). A 5-year course of adjuvant tamoxifen remains the standard therapy for women with hormone receptor-positive breast cancer. The panel recommends that physicians discuss the available information with patients, and, in making a decision, acknowledge that treatment approaches can change over time.

Individual health care providers and their patients will need to come to their own conclusions, with careful consideration of all of the available data. (Specific questions addressed by the panel are summarized in Appendix 3.)
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>39. 2001</td>
<td>Article – NSABP follow up</td>
<td>Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial</td>
<td>FISHER B, JOURNAL OF THE NATIONAL CANCER INSTITUTE 93 : 684</td>
<td>Background: Previously reported information from B-14, a National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized, placebo-controlled clinical trial, demonstrated that patients with estrogen receptor (ER)-positive breast cancer and negative axillary lymph nodes experienced a prolonged benefit from 5 years of tamoxifen therapy. When these women were rerandomized to receive either placebo or more prolonged tamoxifen therapy, they obtained no additional advantage from tamoxifen through 4 years of follow-up. Because the optimal duration of tamoxifen treatment continues to be controversial and because there have been 3 more years of follow-up and a substantial increase in the number of events since our last report, an update of the B-14 study is appropriate. Methods: Patients (n = 1172) who had completed 5 years of tamoxifen therapy and who were disease free were rerandomized to receive placebo (n = 579) or tamoxifen (n = 593). Survival, disease-free survival (DFS), and relapse-free survival (RFS) were estimated by the Kaplan-Meier method; the differences between the treatment groups were assessed by the log-rank test. Relative risks of failure (with 95% confidence intervals) were determined by the Cox proportional hazards model. P values were two-sided. Results: Through 7 years after reassignment of tamoxifen-treated patients to either placebo or continued tamoxifen therapy, a slight advantage was observed in patients who discontinued tamoxifen relative to those who continued to receive it: DFS = 82% versus 78% (P = .03), RFS = 94% versus 92% (P = .13), and survival = 94% versus 91% (P = .07), respectively. The lack of benefit from additional tamoxifen therapy was independent of age or other characteristics. Conclusion: Through 7 years of follow-up after rerandomization, there continues to be no additional benefit from tamoxifen administered beyond 5 years in women with ER-positive breast cancer and negative axillary lymph nodes.</td>
</tr>
<tr>
<td>40. 2001</td>
<td>Article – clinical update</td>
<td>Aromatase inhibitors in the treatment and prevention of breast cancer</td>
<td>GOSS PE, JOURNAL OF CLINICAL ONCOLOGY 19 : 881</td>
<td>Purpose: The purpose of this article is to provide an overview of the current clinical status and possible future applications of aromatase inhibitors in breast cancer. Methods: A review of the literature on the third-generation aromatase inhibitors was conducted. Some data that have been presented but not published are included. In addition, the designs of ongoing trials with aromatase inhibitors are outlined and the implications of possible results discussed. Results: All of the third-generation oral aromatase inhibitors-letrozole, anastrozole, and vorozole (nonsteroidal, type II) and exemestane (steroidal, type I) have now been tested in phase III trials as second-line treatment of postmenopausal hormone-dependent breast cancer. They have shown clear superiority compared with the conventional therapies and are therefore considered established second-line hormonal agents. Currently, they are being tested as first-line therapy in the metastatic, adjuvant, and neoadjuvant settings. Preliminary results suggest that the inhibitors might displace tamoxifen as first-line treatment, but further studies are needed to determine this. Conclusion: The role of aromatase inhibitors in premenopausal breast cancer and in combination with chemotherapy and other anticancer treatments are areas of future exploration. The ongoing adjuvant trials will provide important data on the long-term safety of aromatase inhibitors, which will help to determine their suitability for use as chemopreventives in healthy women at risk of developing breast cancer.</td>
</tr>
<tr>
<td>41. 2001</td>
<td>Article – pilot study of a bone and lipid (meeting)</td>
<td>A pilot prevention study of the aromatase inhibitor letrozole: effects on breast cell proliferation and serum lipid profile in postmenopausal women with breast cancer</td>
<td>HARPER WAYNE C, BREST CANCER RESEARCH AND</td>
<td>Marsden Hospital, London, United Kingdom. Circumstantial data strongly support the concept that suppression of plasma oestrogen (E) levels in postmenopausal women (PMW) would lead to a reduced risk of breast cancer. Aromatase inhibitors (AI) are therefore being considered for evaluation in this setting. Third generation AIs, e.g. letrozole, are well tolerated and anticipated to have less thromboembolic complications and no stimulatory endometrial effects compared with tamoxifen, but E-deprivation may have detrimental effects on other tissues, e.g. bone. A</td>
</tr>
</tbody>
</table>
Letrozole is a competitive aromatase inhibitor. This double-blind, randomised, multicentre endocrine trial was carried out to evaluate the endocrine effects of two doses of letrozole, 0.5 mg versus 2.5 mg orally daily, in postmenopausal advanced breast cancer patients progressing after tamoxifen. The pharmacokinetics of letrozole was also assessed. 46 patients entered the trial, 22 on letrozole 0.5 mg and 24 on 2.5 mg. A significant effect on proliferation of letrozole may be due to the normal breast being relatively insensitive to the low levels of E2 in PMW but this does not discount letrozole’s potential utility as a chemopreventive. Increases in Ctx indicate an increase in bone resorption that may need to be addressed in some women if AIs are to be successful prophylactic agents for breast cancer.

CONCLUSIONS. Sufficient tissue can be obtained from core-cut biopsies from the normal breast of PMW not on HRT, but previously treated for benign disease, DCIS, LCIS or from a volunteer study was undertaken to evaluate the effects of the AI letrozole 2.5mg/d on tissue biomarkers (Kb67, ER) and serum Es, lipids, IgF-1 & products of bone metabolism (Cxt) in healthy PMW. Thirty-two PMW not on HRT, but previously treated for benign disease, DCIS, LCIS or from a 14 gauge corecut needle under ultrasound guidance (≤ 7 cores through one site). Twentynine women completed the study. E2 was significantly suppressed (p<0.001) except in 2 patients, who were excluded from subsequent analyses for presumed non-compliance. IgF-1 and lipids showed no significant change (n=27) but Cxt showed a significant rise (p=0.02) from 1900 to 2369 pmol/l (means) after 3 months. Proliferation (Kb67) of normal epithelial cells was estimated by a novel dual staining methodology: there was a mean 23% fall in Kb67 values during treatment from a mean 1.28 to 0.99 (n=24) but this was not statistically significant. ER did not change significantly over the 3 months. CONCLUSIONS. Sufficient tissue can be obtained from core-cut biopsies from the normal breast of PMW to evaluate biomarkers. The lack of a significant effect on proliferation of letrozole may be due to the normal breast being relatively insensitive to the low levels of E2 in PMW but this does not discount letrozole’s potential utility as a chemopreventive. Increases in Ctx indicate an increase in bone resorption that may need to be addressed in some women if AIs are to be successful prophylactic agents for breast cancer.

To determine the effects of aromatase inhibitors on oestrogen uptake, in situ aromatase activity and endogenous oestrogens in the breast, these being compatible with the clinico-pathological changes which occur with treatment. (C) 

Local endocrine effects of aromatase inhibitors within the breast

To determine the effects of aromatase inhibitors on oestrogen uptake, in situ aromatase activity and endogenous oestrogens in the breast. Postmenopausal women with large primary ER-rich breast cancers have been treated neoadjuvantly for 3 months with either letrozole (2.5 or 10 mg daily) or anastrozole (1 or 10 mg daily) or exemestane (25 mg daily). Patients were given an infusion of H-3-androstenedione and C-14-oestrone for 18 h before and at the end of the study period. Blood, tumour and non-malignant breast were taken immediately after infusion; oestrogens were extracted and purified. Tumour volume was measured before and during treatment at monthly intervals so that endocrinological changes could be related to clinical response. Treatment with each of the aromatase inhibitors was associated with a profound reduction in peripheral aromatase (as monitored by the level of plasma 3 H-oestrone). There was no consistent effect on uptake of radioactively labelled oestrone into breast tumours but a tendency for levels to increase after treatment in non-malignant breast. Conversely, therapy was associated with a marked inhibition of in situ oestrogen synthesis in both tumour and non-malignant breast (in occasional tissues, inhibitors appeared to be less effective but the effect was not related to clinical or pathological responses). Similar decreases were apparent in endogenous levels of oestrone and oestradiol. The absence of in situ aromatase activity tended to be associated with lack of clinical response to aromatase inhibition but the relationship was not absolute, limiting the utility of measurements of tumour aromatase as a predictive indices. Ex vivo studies of tissue aromatase indicated that such measurements consistently underestimate the inhibitory potential of reversible non-steroidal agents (and occasionally paradoxical in vitro increases in aromatase activity were seen with treatment). However, in situ assays demonstrate that new aromatase inhibitors such as anastrozole, exemestane and letrozole have profound effects on the local endocrinology within the postmenopausal breast, these being compatible with the clinico-pathological changes which occur with treatment. (C)

Effect of age and single versus multiple dose pharmacokinetics of letrozole (Femara(R)) in breast cancer patients

Letrozole (trademark Femara(R)) is a new orally active, potent and selective aromatase inhibitor for the hormonal treatment of advanced breast cancer in postmenopausal women. The pharmacokinetics of letrozole and the suppression of peripheral oestrogens were studied in 28 breast cancer patients after a single dose and at steady state. The pharmacokinetics of two distinct age groups (greater than or equal to 50, less than or equal to 65, N = 15 and greater than or equal to 70 years old, N = 9) were compared. There were no significant differences in area under the curve (AUC) or terminal half-life between the two age groups, neither after a single dose nor at steady state. However, when comparing steady state to single dose kinetics, half-life and AUC increased significantly by 42% (90% CI: 1.13,1.78) and 28% (90% CI: 1.12, 1.47), respectively. This deviation from linearity was probably due to a partial saturation of alloinhibition of the dominant metabolic clearance mechanism of letrozole. At steady state, approximately 70% of the administered dose was excreted in urine as unchanged letrozole (6.0 +/- 3.8%) or as the glucuronide of the major, pharmacologically inactive metabolite CGP44645 (64.2 +/- 22.7%). A single dose of letrozole caused suppression of serum estrogen levels close to the quantification limit of the assay. No difference between single dose suppression and suppression at steady state could be detected.
significant suppression of oestrone and oestradiol levels was achieved by both letrozole doses. Neither letrozole dose induced any changes in cortisol and aldosterone production at rest or after Synacthen stimulation. Androstenedione, testosterone, 17α-OH progesterone, triiodothyronine (T3) thyroxine, (T4) and thyroid-stimulating hormone (TSH) plasma levels did not show any significant changes. Sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels increased significantly over time. Plasma letrozole concentrations increased until reaching steady-state values after 1 month at the dose of 0.5 mg and after 2 months at 2.5 mg. In conclusion, both letrozole doses suppressed oestrogen levels without affecting adrenal activity.

The trials that have been performed compare each agent to megestrol acetate, and letrozole and vorozole to aminogluthimide. Although the studies are not directly comparable due to differing study designs and patient populations, it has been demonstrated each of these drugs provides single agent, once-daily, oral palliation of hormone-responsive, post-menopausal metastatic breast cancer. Letrozole is clearly more effective than megestrol acetate, and anastrozole and vorozole are possibly so. All three are better tolerated than the progestins, particularly in terms of weight gain. Both letrozole and vorozole are significantly more effective, and better tolerated than aminogluthimide. Overall, most this recent generation of aromatase inhibitors is a clear improvement on our current standard second-line therapies.

In 1999, tamoxifen remains the first choice in the hormonal therapy of breast cancer. Following tamoxifen failure, the optimal second-line hormonal therapy remains undefined, but aminogluthimide and megestrol acetate are no longer optimal therapy in this setting. The third-generation non-steroidal aromatase inhibitors must now be compared to each other, to the steroidal aromatase inhibitors, and each is superior to previous generations in terms of potency and selectivity.

We have previously established a model for postmenopausal, hormone-dependent breast cancer in nude mice which is responsive to both antiestrogens and aromatase inhibitors. In this model, MCF-7 human breast carcinoma cells transfected with the aromatase gene (MCF-7(ACA)) synthesize sufficient estrogen to form ovariectomized nude mice. In the present study we used this intratumoral aromatase model to investigate the effects on tumor growth of the new nonsteroidal aromatase inhibitors letrozole (CGS 20,267) and anastrozole (ZD 1003) and the antiestrogens tamoxifen (ICI 47,474) and faslodex (ICI 182,780). Furthermore, we determined whether the inhibition of estrogen synthesis together with inhibition of estrogen action would be more effective in controlling breast tumor growth. The results of our studies indicate that the aromatase inhibitors anastrozole and letrozole, as well as the new pure antiestrogen faslodex, have potent antitumor effects in the mouse model. In the treatment of mice with mammary tumors, letrozole was more effective in suppressing tumor growth than anastrozole. This was consistent with the Ki values of these inhibitors against placental aromatase and the IC50 values in cell culture (MCF-7(ACA)), which indicated the greater potency of letrozole as an aromatase inhibitor. Letrozole also had greater antitumor effects than tamoxifen and faslodex. The antitumor effect of letrozole was substantial, making it difficult to detect any additional effect on the tumors when letrozole was combined with the antiestrogens. However, the combined treatment of anastrozole + tamoxifen and anastrozole + faslodex also did not increase efficacy compared to the aromatase inhibitor alone. In addition, combining the two aromatase inhibitors did not suppress tumor growth more effectively than faslodex alone. Our results show that treatment with the combinations of aromatase inhibitors with either tamoxifen or faslodex are not more effective in blocking estrogen stimulation of tumor growth than the aromatase inhibitors alone.
paradoxically high aromatase activity; this appears to be caused by the reversible nature of the inhibition, coupled with induction/stabilization of the aromatase enzyme. To assess in situ effects within the breast, postmenopausal women with large primary breast cancers have been treated neoadjuvantly with aromatase inhibitors using a protocol that included (i) breast biopsy before treatment, (ii) definitive surgery after 3 months of treatment and (iii) infusion of [H-3]androstenedione and [C-14]progesterone in the 18 h immediately before biopsy and surgery. With this study design, it has been shown that drugs such as letrozole profoundly inhibit in situ aromatase activity and reduce endogenous oestrogens within the breast.

48. 1998 Article - trial overview Tamoxifen for early breast cancer: An overview of the randomised trials CLARKE M LANCET 351 : 1451 Background. There have been many randomised trials of adjuvant tamoxifen among women with early breast cancer, and an updated overview of their results is presented.

Methods. In 1995, information was sought on each woman in any randomised trial that began before 1990 of adjuvant tamoxifen versus no tamoxifen before recurrence. Information was obtained and analysed centrally on each of 37000 women in 55 such trials, comprising about 87% of the worldwide evidence. Compared with the previous such overview, this approximately doubles the amount of evidence from trials of about 5 years of tamoxifen and, taking all trials together, on events occurring more than 5 years after randomisation.

Findings. Nearly 8000 of the women had a low, or zero, level of the oestrogen-receptor protein (ER) measured in their primary tumour. Among them, the overall effects of tamoxifen appeared to be small, and subsequent analyses of recurrences and total mortality are restricted to the remaining women (18000 with ER-positive tumours, plus nearly 12000 more with untested tumours, of which an estimated 8000 would have been ER-positive). For trials of 1 year, 2 years, and about 5 years of adjuvant tamoxifen, the proportional recurrence reductions produced among these 30000 women during about 10 years of follow-up were 21% (SD 3), 29% (SD 2), and 47% (SD 3), respectively, with a highly significant trend towards greater effect with longer treatment (x(2)(1) = 52.0, 2p < 0.00001). The corresponding proportional mortality reductions were 12% (SD 3), 17% (SD 3), and 26% (SD 4), respectively, and again the test for trend was significant (x(1) = 8.8, 2p = 0.003). The absolute improvement in recurrence was greater during the first 5 years, whereas the improvement in survival grew steadily larger throughout the first 10 years. The proportional mortality reductions were similar for women with node-positive and node-negative disease, but the absolute mortality reductions were greater in node-positive women. In the trials of about 5 years of adjuvant tamoxifen the absolute improvements in 10-year survival were 10.9% (SD 2.5) for node-positive (81.4% vs 50.5% survival, 2p < 0.00001) and 5.6% (SD 1.3) for node-negative (78.8% vs 73.3% survival, 2p < 0.00001). These benefits appeared to be largely irrespective of age, menopausal status, daily tamoxifen dose (which was generally 20 mg), and of whether chemotherapy had been given to both groups. In terms of other outcomes among all women studied in these 30000 women during about 10 years of follow-up were 21% (SD 3), 29% (SD 2), and 47% (SD 3), respectively, with a highly significant trend towards greater effect with longer treatment (x(2)(1) = 52.0, 2p < 0.00001). The corresponding proportional mortality reductions were 12% (SD 3), 17% (SD 3), and 26% (SD 4), respectively, and again the test for trend was significant (x(1) = 8.8, 2p = 0.003). The absolute improvement in recurrence was greater during the first 5 years, whereas the improvement in survival grew steadily larger throughout the first 10 years. The proportional mortality reductions were similar for women with node-positive and node-negative disease, but the absolute mortality reductions were greater in node-positive women. In the trials of about 5 years of adjuvant tamoxifen the absolute improvements in 10-year survival were 10.9% (SD 2.5) for node-positive (81.4% vs 50.5% survival, 2p < 0.00001) and 5.6% (SD 1.3) for node-negative (78.8% vs 73.3% survival, 2p < 0.00001). These benefits appeared to be largely irrespective of age, menopausal status, daily tamoxifen dose (which was generally 20 mg), and of whether chemotherapy had been given to both groups.

49. 1998 Article – Tamoxifen NSBBP P-1 study Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study FISHER B JOURNAL OF THE NATIONAL CANCER INSTITUTE 90 : 1371 Background: The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant breast therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992. Methods: Women (N = 13388) at increased risk for breast cancer because they (i) were 60 years of age or older, (ii) had a disease of other types than breast cancer, (iii) had a history of familial breast cancer, (iv) had a prior history of breast cancer, (v) had a family history of breast cancer, (vi) had a history of endometrial cancer, (vii) had a history of breast cancer, and (viii) had a history of endometrial cancer. Patients were randomised to receive tamoxifen or placebo. The primary endpoint was the occurrence of breast cancer in the contralateral breast. Results: The proportion of women who developed breast cancer in the contralateral breast was 3.8% in the tamoxifen group and 6.8% in the placebo group (2p = 0.008). The difference was statistically significant and persisted throughout the study. The relative risk of breast cancer in the contralateral breast was 0.57 (95% CI: 0.44, 0.75). Conclusions: Tamoxifen significantly reduces the risk of breast cancer in the contralateral breast. This effect is independent of age, menopausal status, and menopausal status. The absolute reduction in breast cancer incidence in the contralateral breast was 3.8% in the tamoxifen group and 6.8% in the placebo group. The relative risk of breast cancer in the contralateral breast was 0.57 (95% CI: 0.44, 0.75).
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. 1998</td>
<td>Article - review</td>
<td>Letrozole - A review of its use in postmenopausal women with advanced breast cancer</td>
<td>LAMB HM DRUGS 56 : 1125 1998</td>
<td>Letrozole is an oral reversible nonsteroidal aromatase inhibitor. Clinical tracer studies show that it inhibits peripheral aromatase by over 98% and suppresses blood and urinary estrogen levels by over 95% after 2 weeks of treatment in postmenopausal women. Letrozole also significantly inhibits intratumoral aromatase in vivo. The action of letrozole appears to be selective for aromatase; long term administration did not affect basal levels of 17 alpha-hydroxyprogesterone or aldosterone, although slight decreases in cortisol levels were observed in 2 studies, these did not appear to be clinically significant. In 2 phase Ib/III trials, letrozole 2.5 mg/day achieved objective response rates of 19.5 and 23.6% which were sustained for a median duration of 24 and 33 months, respectively. The median duration of response compared favourably with both comparator agents, aminoglutethimide and megestrol (15 and 15 months, respectively), as did objective response rates (12.4 and 16.4%). Letrozole 2.5 mg/day was associated with an increase in median survival time of 8 and 3 months compared with aromatase inhibitors and megestrol, respectively, according to analyses of overall survival. Letrozole 2.5 mg/day was significantly superior to both comparators with respect to duration of response and aromatase inhibition with respect to survival. Letrozole has a good short term tolerability profile. The adverse events most commonly in association with letrozole 2.5 mg/day in the 2 phase Ib/III trials were headache (1.1 and 7%), nausea (6 and 10.3%), fatigue (3.2 and 5%), hot flushes (4.9 and 5%) and peripheral oedema (6%). Events were usually mild to moderate in severity; adverse events necessitated discontinuation of treatment in 3% of letrozole 2.5 mg/day recipients. Conclusions: Letrozole, in common with vorozole and anastrozole, offers greater selectivity and potency of aromatase inhibition than the prototype aromatase inhibitor, aminoglutethimide, and can be administered once daily. Available clinical data suggest that letrozole achieves a significantly longer duration of response than megestrol and aminoglutethimide and longer overall survival than aromatase inhibitors. However, direct comparisons are required to distinguish between the newer aromatase inhibitors. For this reason, letrozole should be recommended as a second-line treatment in postmenopausal women with advanced breast cancer whose disease has progressed on or failed to respond to anastrozole therapy.</td>
</tr>
<tr>
<td>51. 1998</td>
<td>Article – nude mouse</td>
<td>The effects of aromatase inhibitors and antiestrogens in the nude mouse model</td>
<td>LU Q BREAST CANCER RESEARCH AND TREATMENT 50 : 63</td>
<td>The effects of antiestrogens, tamoxifen and ICI 182.780, and aromatase inhibitors, arimide (anastrozole ZD1033) and letrozole (CGS 20,287), on the growth of tumors were studied in nude mice. In this model, estrogen dependent MCF-7 human breast cancer cells stably transfected with the aromatase gene were inoculated in four sites per mouse. Sufficient estrogen is produced from aromatization of androstenedione supplement (0.1 mg/mouse/day) by the cells to stimulate their proliferation, tumor formation, and maintain the uterus similar to that of the intact mouse. Once the tumors reached a measurable size, the mice were injected with antiestrogen or inhibitor for 35-56 days. Tumor volumes were measured</td>
</tr>
</tbody>
</table>

Based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the probability (risk) of occurrence of breast cancer over time. Results: Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided P<0.0001), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50-59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided P<0.002). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Collie’s), and spine fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group (risk ratio = 2.53; 95% confidence interval = 1.35-4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I/locализed disease; no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older. Conclusions: Tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease.
52. Article – dosage + absorption rate

Comparative bioavailability of letrozole under fed and fasting conditions in 12 healthy subjects after a 2 center dot 5 mg single oral administration

SIOUF A
BIOPHARMACEUTICS & DRUG DISPOSITION 18 : 489

Letrozole is a new non-steroidal inhibitor of the aromatase enzyme system. It is currently under development for the treatment of postmenopausal women with advanced breast cancer. To investigate the influence of food on the bioavailability of letrozole, 12 healthy male volunteers were treated under fed and fasted conditions with single oral doses of 2.5 mg letrozole in film-coated tablets. Plasma concentration profiles were determined. No significant difference in the extent of absorption (AUG or AUC(0->8) h) was observed between the two treatments but the rate of letrozole absorption decreased slightly under fed conditions. However, in view of the half-life of about 2 d this small change in the absorption rate is not considered to be of clinical relevance for treatment with repeated administrations.

53. Article Tamoxifen

Five versus more than 5 years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors

FISHER B
JOURNAL OF THE NATIONAL CANCER INSTITUTE 88 : 1529

Background: In 1982, the National Surgical Adjuvant Breast and Bowel Project initiated a randomized, double-blinded, placebo-controlled trial (B-14) to determine the effectiveness of adjuvant tamoxifen therapy in patients with primary operable breast cancer who had estrogen receptor-positive tumors and no axillary lymph node involvement. The findings indicated that tamoxifen therapy provided substantial benefit to patients with early stage disease. However, questions arose about how long the observed benefit would persist, about the duration of therapy necessary to maintain maximum benefit, and about the nature and severity of adverse effects from prolonged treatment. Purpose: We evaluated the outcome of patients in the B-14 trial through 10 years of follow-up. In addition, the effects of 5 years versus more than 5 years of tamoxifen therapy were compared. Methods: In the trial, patients were initially assigned to receive either tamoxifen at 20 mg/day (n = 1404) or placebo (n = 1414). Tamoxifen-treated patients who remained disease free after 5 years of therapy were then reassigned to receive either another 5 years of tamoxifen (n = 322) or 5 years of placebo (n = 321). After the study began, another group of patients who met the same protocol eligibility requirements as the randomly assigned patients were registered to receive tamoxifen (n = 1211). Registered patients who were disease free after 5 years of treatment were also randomly assigned to another 5 years of tamoxifen (n = 261) or to 5 years of placebo (n = 249). To compare 5 years with more than 5 years of tamoxifen therapy, data relating to all patients reassigned to an additional 5 years of the drug were combined. Patients who were not reassigned to either tamoxifen or placebo continued to be followed in the study. Survival, disease-free survival, and distant disease-free survival (relating to failure at distant sites) were found for patients who discontinued tamoxifen therapy or placebo groups, advantages in disease-free survival (96% versus 90%, P = .01) were found for those who discontinued tamoxifen therapy provided substantial benefit to patients with early stage disease. However, questions arose about how long the observed benefit would persist, about the duration of therapy necessary to maintain maximum benefit, and about the nature and severity of adverse effects from prolonged treatment. Purpose: We evaluated the outcome of patients in the B-14 trial through 10 years of follow-up. In addition, the effects of 5 years versus more than 5 years of tamoxifen therapy were compared. Methods: In the trial, patients were initially assigned to receive either tamoxifen at 20 mg/day (n = 1404) or placebo (n = 1414). Tamoxifen-treated patients who remained disease free after 5 years of therapy were then reassigned to receive either another 5 years of tamoxifen (n = 322) or 5 years of placebo (n = 321). After the study began, another group of patients who met the same protocol eligibility requirements as the randomly assigned patients were registered to receive tamoxifen (n = 1211). Registered patients who were disease free after 5 years of treatment were also randomly assigned to another 5 years of tamoxifen (n = 261) or to 5 years of placebo (n = 249). To compare 5 years with more than 5 years of tamoxifen therapy, data relating to all patients reassigned to an additional 5 years of the drug were combined. Patients who were not reassigned to either tamoxifen or placebo continued to be followed in the study. Survival, disease-free survival, and distant disease-free survival (relating to failure at distant sites) were estimated by use of the Kaplan-Meier method; differences between the treatment groups were assessed by use of the logrank test. The relative risks of failure (with 95% confidence intervals [CIs]) were determined by use of the Cox proportional hazards model. Reported P values are two-sided. Results: Through 10 years of follow-up, a significant advantage in disease-free survival (85% versus 77%, P = .003; HR = 0.70; 95% CI = 0.58-0.84), and survival (80% versus 76%, P = .02; relative risk = 0.84; 95% CI = 0.71-0.99) was found for patients in the group first assigned to receive tamoxifen. The survival benefit extended to those 49 years of age or younger and to those 50 years of age or older. Tamoxifen therapy was associated with a 37% reduction in the incidence of contralateral (opposite) breast cancer (P = .007). Through 4 years after the reassignment of tamoxifen-treated patients to either continued-therapy or placebo groups, advantages in disease-free survival (93% versus 86%, P = .003) and distant disease-free survival (96% versus 90%, P = .01) were found for those who discontinued tamoxifen treatment. Survival was 96% for those who discontinued tamoxifen compared with 94% for those who continued tamoxifen treatment (P = .08). A higher incidence of thromboembolic events was seen in tamoxifen-treated patients (through 5 years, 1.7% versus 0.4%). Except for endometrial cancer, the incidence of second cancers was not increased with tamoxifen therapy. Conclusions and Implications: The benefit from 5 years of tamoxifen therapy persists through 10 years of follow-up. No additional advantage is obtained from continuing tamoxifen therapy for more than 5 years.

54. Article –

In vivo measurement of

DOWSETT M

Thirteen postmenopausal women with advanced breast cancer were enrolled in an open randomized Phase I trial of a new p.o. active aromatase

Resource Title
Comparative bioavailability of letrozole under fed and fasting conditions in 12 healthy subjects after a 2 center dot 5 mg single oral administration
Five versus more than 5 years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors
Letrozole is a new non-steroidal inhibitor of the aromatase enzyme system. It is currently under development for the treatment of postmenopausal women with advanced breast cancer. To investigate the influence of food on the bioavailability of letrozole, 12 healthy male volunteers were treated under fed and fasted conditions with single oral doses of 2.5 mg letrozole in film-coated tablets. Plasma concentration profiles were determined. No significant difference in the extent of absorption (AUG or AUC(0->8) h) was observed between the two treatments but the rate of letrozole absorption decreased slightly under fed conditions. However, in view of the half-life of about 2 d this small change in the absorption rate is not considered to be of clinical relevance for treatment with repeated administrations.

Survival, disease-free survival, and distant disease-free survival (relating to failure at distant sites) were found for patients who discontinued tamoxifen therapy or placebo groups, advantages in disease-free survival (96% versus 90%, P = .01) were found for those who discontinued tamoxifen therapy provided substantial benefit to patients with early stage disease. However, questions arose about how long the observed benefit would persist, about the duration of therapy necessary to maintain maximum benefit, and about the nature and severity of adverse effects from prolonged treatment. Purpose: We evaluated the outcome of patients in the B-14 trial through 10 years of follow-up. In addition, the effects of 5 years versus more than 5 years of tamoxifen therapy were compared. Methods: In the trial, patients were initially assigned to receive either tamoxifen at 20 mg/day (n = 1404) or placebo (n = 1414). Tamoxifen-treated patients who remained disease free after 5 years of therapy were then reassigned to receive either another 5 years of tamoxifen (n = 322) or 5 years of placebo (n = 321). After the study began, another group of patients who met the same protocol eligibility requirements as the randomly assigned patients were registered to receive tamoxifen (n = 1211). Registered patients who were disease free after 5 years of treatment were also randomly assigned to another 5 years of tamoxifen (n = 261) or to 5 years of placebo (n = 249). To compare 5 years with more than 5 years of tamoxifen therapy, data relating to all patients reassigned to an additional 5 years of the drug were combined. Patients who were not reassigned to either tamoxifen or placebo continued to be followed in the study. Survival, disease-free survival, and distant disease-free survival (relating to failure at distant sites) were estimated by use of the Kaplan-Meier method; differences between the treatment groups were assessed by use of the logrank test. The relative risks of failure (with 95% confidence intervals [CIs]) were determined by use of the Cox proportional hazards model. Reported P values are two-sided. Results: Through 10 years of follow-up, a significant advantage in disease-free survival (85% versus 77%, P = .003; HR = 0.70; 95% CI = 0.58-0.84), and survival (80% versus 76%, P = .02; relative risk = 0.84; 95% CI = 0.71-0.99) was found for patients in the group first assigned to receive tamoxifen. The survival benefit extended to those 49 years of age or younger and to those 50 years of age or older. Tamoxifen therapy was associated with a 37% reduction in the incidence of contralateral (opposite) breast cancer (P = .007). Through 4 years after the reassignment of tamoxifen-treated patients to either continued-therapy or placebo groups, advantages in disease-free survival (93% versus 86%, P = .003) and distant disease-free survival (96% versus 90%, P = .01) were found for those who discontinued tamoxifen treatment. Survival was 96% for those who discontinued tamoxifen compared with 94% for those who continued tamoxifen treatment (P = .08). A higher incidence of thromboembolic events was seen in tamoxifen-treated patients (through 5 years, 1.7% versus 0.4%). Except for endometrial cancer, the incidence of second cancers was not increased with tamoxifen therapy. Conclusions and Implications: The benefit from 5 years of tamoxifen therapy persists through 10 years of follow-up. No additional advantage is obtained from continuing tamoxifen therapy for more than 5 years.
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Letrozole Phase 1</td>
<td>aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer</td>
<td>CLINICAL CANCER RESEARCH 1 : 1511</td>
<td>inhibitor, CGS 20267 (letrazole). The primary aim of the trial was to assess the impact of two doses of letrozole (0.5 and 2.5 mg/day) on the peripheral aromatization of androstenedione to estrone. An in vivo isotopic technique was used to measure peripheral aromatization in each patient before treatment. The patients were then randomly assigned to one of the two doses, and measurements of aromatization were repeated after 6 weeks. At 0.5 mg and 2.5 mg/day, letrozole inhibited aromatization by 98.4% (97.3 &gt; 99.1) and &gt; 98.9% (98.5 &gt; 99.1) geometric means and ranges, respectively. Plasma estrogen levels were also measured before and during treatment, At the dose of 0.5 mg/day estrone and estradiol levels fell by 82.0% and 84.1% (geometric means), respectively, At the dose of 2.5 mg/day, the estrogens fell by 80.8% and 68.1%, respectively. There were no significant differences between the doses in aromatase inhibition. No formal statistical analysis was performed on the estrogen data. Letrozole is therefore a highly effective inhibitor of aromatase, causing near complete inhibition of the enzyme in peripheral tissues at the doses investigated. The falls in estrogen levels were greater than those seen with earlier generation aromatase inhibitors.</td>
</tr>
<tr>
<td>1995</td>
<td>Article – third generation AI, bioassay</td>
<td>Use of ultrasensitive recombinant cell bioassay to measure estrogen-levels in women with breast cancer receiving the aromatase inhibitor, letrozole</td>
<td>KLEIN KO JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM 80 : 2058</td>
<td>The development of well tolerated, potent, specific, and nontoxic aromatase inhibitors for the treatment of postmenopausal women with estrogen-dependent breast cancer has been a major goal of recent studies. The third generation inhibitors now under investigation are nearly 10,000-fold more potent than first generation compounds. Currently available RIAs for plasma estradiol lack sufficient sensitivity to measure levels during aromatase inhibition and, thus, to assess drug potency precisely. The availability of an ultrasensitive bioassay for estradiol provided the opportunity to accurately assess the potency of a new third generation triazole aromatase inhibitor, letrozole (CGS 20267). We used this assay to measure estradiol levels in 14 women with metastatic breast cancer given letrozole at doses of 100 μg to 5.0 mg/day over a 1a-week period. The lack of differences between doses and sampling times allowed pooling of data. Basal estradiol levels of 7.2 +/- 1.9 pmol/L (mean +/- SEM, 1.95 +/- 0.52 pg/mL) fell to 0.26 +/- 0.11 pmol/L (0.07 +/- 0.03 pg/mL) during the first 6 weeks of therapy and to 0.46 +/- 0.18 pmol/L (0.13 +/- 0.05 pg/mL) during the second 6 weeks of therapy. Although plasma estradiol levels measured by RIA were significantly correlated with levels measured by bioassay (r = 0.79; P &lt; 0.01), the degree of suppression assessed by the bioassay (95 +/- 2% after 6 weeks) was greater than that determined by the RIA (81 +/- 4%), presumably due to improved ability to measure very low estradiol levels. We conclude that plasma estradiol is suppressed by letrozole to lower levels than previously observed, with equivalent suppression at all doses studied. A slight, although not statistically significant, rebound in estradiol levels occurs during the second 6 weeks of therapy compared to the first 6 weeks. Maximum inhibition of aromatase is achieved at letrozole doses as low as 100 μg.</td>
</tr>
<tr>
<td>1995</td>
<td>Article – MCF-7 model</td>
<td>An in-vivo model of intratumoral aromatase using aromatase-transfected mcf7 human breast-cancer cells</td>
<td>LEE K INTERNATIONAL JOURNAL OF CANCER 62 : 297</td>
<td>About two-thirds of human breast carcinomas contain detectable levels of aromatase, the enzyme which converts androgens to oestrogens. Assessment of the importance of this enzyme to breast cancer growth has been hampered by the absence of an adequate model system. We have previously reported that MCF7 human hormone-dependent breast cancer cells transfected with human aromatase cDNA (Arom1 cells) showed a growth response in vitro to exogenous androgens and this effect was blocked by aromatase inhibitors. We report here our use of these cells to develop a xenograft model in athymic nude mice. Neither MCF7 cells nor Arom1 cells formed tumours in oophorectomised (ovx) nude mice unless provided with oestradiol (E2) support. Once established, Arom1, but not MCF7, tumours could be grown in ovx females supplemented with androstenedione (Delta 4A). The mean plasma level of Delta 4A was 14 nmol/L in supplemented animals and &lt; 0.5 nmol/L in unsupplemented animals. Similarly, unsupplemented male nude mice were able to support the growth of Arom1 tumours but not MCF7 tumours. The potent and highly specific aromatase inhibitor CGS20287 (letrazole) significantly decreased tumour growth at 2 mg/kg/day and completely inhibited growth at 20 mg/kg/day in Delta 4A-supplemented but not E2-supplemented animals. Our results indicate that Delta 4A-dependent growth of Arom1 tumours in vivo is mediated through the action of intratumoral aromatase. This model should allow an assessment of the critical levels of aromatase required for tumour growth support. (C)</td>
</tr>
<tr>
<td>1995</td>
<td>Article – Letrozole Phase 1</td>
<td>Letrozole (CGS 20267) - a phase I study of a new potent oral aromatase inhibitor of breast-cancer</td>
<td>LIPTON A CANCER 75 : 2132</td>
<td>Background. Letrozole (CGS 20267), a triazole derivative, is a new, once-daily, oral nonsteroidal inhibitor of aromatase activity. Methods. In this Phase I trial, 23 heavily pretreated postmenopausal patients with metastatic breast cancer received letrozole at doses ranging from 0.1 to 5.0 mg once daily.</td>
</tr>
</tbody>
</table>
Results. No hematologic, biochemical, or significant clinical toxicity was encountered. Serial steroid measurements were determined in 19 of these patients. Letrozole at all doses tested produced a marked suppression of plasma estrone, estradiol, estrone sulfate, and urine estrone and estradiol. This was observed within 24 hours of the initial dose of letrozole and resulted in a greater than 90% suppression of plasma and urinary estrogen levels within 2 weeks. Letrozole appears to be highly selective in its action and does not compromise glucocorticoid or mineralocorticoid production or thyroid function. Of the 21 evaluable patients, there were 2 with partial responses and 7 with stable disease.

Conclusions. Letrozole is a well tolerated, potent, and specific inhibitor of estrogen biosynthesis in postmenopausal patients with metastatic breast cancer.

59. 1995
Article - MCF-7 model
Estrogen deprivation causes estradiol hypersensitivity in human breast-cancer cells
MASAMURA S
JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM 80 : 2918
Genetic and environmental factors can modulate the level of sensitivity to various hormones, including estrogens. Enhanced sensitivity to estradiol (E2) has been demonstrated in several biological conditions, such as in sheep during the nonbreeding season, in untreated patients with Turner’s syndrome, and in the pubertal state in normal girls. We postulated that secondary responses to hormonal therapy in patients with breast cancer could also result from enhanced E2 sensitivity, developing as an adaptive mechanism to E2 deprivation. The present study used the MCF-7 human breast cancer cell line as a model system to test the concept that enhanced sensitivity to E2 may occur as a result of adaptation to low E2 levels. After depriving MCF-7 cells of estrogens in tissue culture medium for periods of 1-6 months, we established conditions under which replication could be stimulated maximally by 10(-14)-10(-15) mol/L E2. In contrast, wild-type cells not exposed to estrogen deprivation required 10(-10) mol/L E2 to grow at the same rate. Further, the concentration of the antiestrogen, ICI 164384, needed to inhibit growth by 50% in estrogen-deprived cells was much lower than that required in wild-type cells (i.e. 10(-15) vs. 10(-9) mol/L). Nude mice implanted with these estrogen-deprived cells demonstrated an earlier appearance of palpable tumors in response to E2 than animals bearing wild-type cells. Reexposure to 10(-10)-10(-9) mol/L E2, either in vivo or in vitro, returned these cells to the level of estrogen sensitivity observed in wild-type cells. Taken together, these observations suggest that breast cancer cells can adapt to low levels of estrogens by enhancing their sensitivity to E2.

60. 1993
Article – Phase 1
CGS 20267
Phase-I study of the oral nonsteroidal aromatase inhibitor-cgs-20267 in postmenopausal patients with advanced breast cancer
IVESON TJ
CANCER RESEARCH 53 : 266
A phase I study was performed of CGS 20267, an oral nonsteroidal, highly potent, and selective aromatase inhibitor, in 21 postmenopausal patients with advanced breast cancer. The patients were recruited in 3 successive groups of 7, receiving 0.1, 0.5, and 2.5 mg p.o./day, respectively. All patients had received at least one prior endocrine treatment (range, 1-4), and six patients had received prior chemotherapy. The treatment was very well tolerated, and no toxicity was seen at any of the three doses. There was a statistically significant suppression of estradiol (E2) and estrone (E1) levels by 74% and 79% from baseline levels, respectively (P < 0.0001). Suppression occurred in all three patient groups, with many patients having serum concentrations of estradiol and estrone, which were below the limit of detection of the assays (3 and 10 pM, respectively), which corresponds to a maximum measurable estrogen suppression of 86%. CGS 20267 had no significant effect on serum levels.
<table>
<thead>
<tr>
<th>Year Published</th>
<th>Legend Guide</th>
<th>Resource Title</th>
<th>Primary Author and Journal Reference</th>
<th>Resource Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Article – tamoxifen resistance</td>
<td>Mechanisms for tamoxifen resistance in breast-cancer  - possible role of tamoxifen metabolism</td>
<td>OSBORNE CK JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY 47 : 83</td>
<td>Potential mechanisms for tamoxifen resistance include loss or alteration in estrogen receptor or other transcription factors and altered tamoxifen pharmacology. Using an experimental model, we have previously demonstrated that one form of tamoxifen resistance is related to the acquired ability of tamoxifen to stimulate tumor growth. These tamoxifen-stimulated tumors contain a reduced tamoxifen concentration and an altered metabolite profile suggesting that accumulation of more estrogenic metabolites could explain this phenomenon. However, in vivo treatment of nude mice carrying tamoxifen-stimulated tumors with fixed ring non-isomerizable analogs, or other analogs resistant to conversion to metabolite E (a full estrogen), still resulted in tumor growth stimulation. Growth of these tamoxifen-stimulated tumors was inhibited by a pure steroidal antiestrogen,ICI 182,780, suggesting that this drug should be investigated in patients with tamoxifen resistance. These tamoxifen-stimulated tumors could be further stimulated by estrogen replenishment, and estrogen stimulation was blocked by tamoxifen, indicating that tamoxifen has both agonist and antagonist properties in these tumors. Our data suggest that although tamoxifen-stimulated tumors display a markedly altered metabolite profile, isomerization or metabolism of tamoxifen does not fully explain the development of tamoxifen-stimulated growth. The mechanisms by which tamoxifen acquires more potent in vivo agonist properties over time remains to be defined.</td>
</tr>
<tr>
<td>1992</td>
<td>Article review trials</td>
<td>Systemic treatment of early breast-cancer by hormonal, cytotoxic, or immune therapy - 133 randomized trials involving 31000 recurrences and 24000 deaths among 75000 women .2</td>
<td>ABE O LANCET 339 : 71</td>
<td>Discusses results of women with breast cancer in trials of long-term polychemotherapy vs. trials with no chemotherapy and in randomized trials of preoperative, perioperative or prolonged single-agent chemotherapy. Reports that an overview of the result of these trials provides statistically significant evidence that some forms of chemotherapy can affect both recurrence and survival. Absolute reductions in long term risk: Results of immunotherapy. More.</td>
</tr>
<tr>
<td>1992</td>
<td>Article – tamoxifen bone density</td>
<td>Effects of tamoxifen on bone-mineral density in postmenopausal women with breast-cancer</td>
<td>LOVE RR NEW ENGLAND JOURNAL OF MEDICINE 326 : 852</td>
<td>Background and Methods. Tamoxifen, a synthetic antiestrogen, increases disease-free and overall survival when used as adjuvant therapy for primary breast cancer. Because it is given for long periods, it is important to know whether tamoxifen affects the skeleton, particularly since it is used extensively in postmenopausal women who are at risk for osteoporosis. Using photon absorptiometry, we studied the effects of tamoxifen on the bone mineral density of the lumbar spine and radius and on biochemical measures of bone metabolism in 140 postmenopausal women with axillary-node-negative breast cancer, in a two-year randomized, double-blind, placebo-controlled trial. Results. In the women given tamoxifen, the mean bone mineral density of the lumbar spine increased by 0.61 percent per year, whereas in those given placebo it decreased by 1.00 percent per year (P &lt; 0.001). Radial bone mineral density decreased to the same extent in both groups. In a subgroup randomly selected from each group, serum osteocalcin and alkaline phosphatase concentrations decreased significantly in women given tamoxifen (P &lt; 0.001 for each variable), whereas serum parathyroid hormone and 1,25-dihydroxyvitamin D concentrations did not change significantly in either group. Conclusions. In postmenopausal women, treatment with tamoxifen is associated with preservation of the bone mineral density of the lumbar spine. Whether this favorable effect on bone mineral density is accompanied by a decrease in the risk of fractures remains to be determined.</td>
</tr>
<tr>
<td>1991</td>
<td>Estrogen-receptor variants in clinical breast-cancer</td>
<td>MCGUIRE WL</td>
<td>We have used the screening techniques of chemical mismatch cleavage, single stranded conformational polymorphism, and gel retardation to discover a number of estrogen receptor DNA variants in clinical breast cancer tissues. We have found basepair insertions, transitions, and</td>
<td></td>
</tr>
<tr>
<td>Year Published</td>
<td>Legend Guide</td>
<td>Resource Title</td>
<td>Primary Author and Journal Reference</td>
<td>Resource Abstract</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>1990</td>
<td>Article – tamoxifen lipid effect</td>
<td>Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast-cancer</td>
<td>LOVE RR JOURNAL OF THE NATIONAL CANCER INSTITUTE 82 : 1327</td>
<td>We conducted a 2-year, randomized, double-blind, placebo-controlled toxicity trial of therapy with tamoxifen (10 mg twice a day) in 140 postmenopausal women with a history of breast cancer and histologically negative axillary lymph nodes. These women had been treated with surgery or without radiotherapy. At a 3-month evaluation, tamoxifen-treated women showed a significant decrease in fasting plasma levels of total cholesterol and low-density lipoprotein (LDL) cholesterol, which persisted at 6- and 12-month evaluations. During the first 12 months, plasma triglyceride levels increased; small but significant decreases in high-density lipoprotein cholesterol (HDL) were observed in tamoxifen-treated women, but ratios of total cholesterol to HDL cholesterol and of LDL to HDL cholesterol changed favorably. While data relating lipid/lipoprotein profiles and cardiovascular disease are limited in women, current evidence suggests that total cholesterol and possibly low-density lipoprotein cholesterol are risk factors. We conclude that during the first 12 months of treatment, tamoxifen exerts a favorable effect on the lipid profile in postmenopausal women with early stage breast cancer.</td>
</tr>
<tr>
<td>1990</td>
<td>Article – endocrine effect</td>
<td>The clinical and endocrine effects of 4-hydroxyandrostenedione alone and in combination with goserelin in premenopausal women with node-positive breast cancer</td>
<td>STEIN RC BRITISH JOURNAL OF CANCER 62 : 679</td>
<td>The aromatase inhibitor, 4-hydroxyandrostenedione (4OHA) is an effective treatment for advanced post-menopausal breast cancer. The clinical and endocrine effects of 4OHA treatment were studied in five pre and perimenopausal women with metastatic breast cancer. Serum oestradiol levels were not significantly reduced as a result of treatment with 500 mg of 4OHA by weekly i.m. injections and no patient had a tumour response. Four patients were subsequently treated with the luteinising hormone releasing hormone (LHRH) analogue, goserelene, and three had objective responses. The endocrine effects of combined treatment with goserelin (Zoladex), and 4OHA were studied in a further five premenopausal women. Serum oestradiol levels after treatment with goserelin alone were typical of post-menopausal women. Addition of 4OHA to the range observed in post-menopausal patients treated with further suppression of oestradiol to within the range observed in post-menopausal patients treated with 4OHA. Six patients whose tumours had regressed as a result of goserelin treatment and who subsequently relapsed were then given combined treatment. Four of the six experienced a second remission. We conclude that while 4OHA alone is unlikely to be a satisfactory treatment for premenopausal patients with advanced breast cancer, 4OHA in combination with goserelin leads to profound suppression of oestradiol. The combination of LHRH analogue and aromatase inhibitor may prove to be a superior treatment to LHRH analogue alone in these patients.</td>
</tr>
<tr>
<td>1989</td>
<td>Article – randomized clinical trial of tamoxifen estrogen</td>
<td>A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor positive tumors</td>
<td>FISHER B NEW ENGLAND JOURNAL OF MEDICINE 320 : 479</td>
<td>We conducted a randomized, double-blind, placebo-controlled trial of postoperative therapy with tamoxifen (10 mg twice a day) in 2644 patients with breast cancer, histologically negative axillary nodes, and estrogen-receptor-positive (greater than or equal to 10 fmol) tumors. No survival advantage was observed during four years of follow-up (92 percent for placebo vs. 93 percent for tamoxifen; P = 0.3). There was a significant prolongation of disease-free survival among women treated with tamoxifen, as compared with those receiving placebo (83 percent vs. 77 percent; P less than 0.0001). This advantage was observed in both the patients less than or equal to 49 years old (P = 0.0005) and those greater than or equal to 50 (P = 0.0008), particularly in the former, among whom the rate of treatment failure was reduced by 44 percent. Multivariate analysis indicated that all subgroups of patients benefited. Tamoxifen significantly reduced the rate of treatment failure at local and distant sites, tumors in the opposite breast, and the incidence of tumor recurrence after lumpectomy and breast irradiation. The benefit was</td>
</tr>
</tbody>
</table>
Year Published | Legend Guide | Resource Title | Primary Author and Journal Reference | Resource Abstract
--- | --- | --- | --- | ---
69. | 1988 | Article – tamoxifen growth tumors in mice | GOTTARDIS MM | Long-term tamoxifen (TAM) therapy was examined in athymic mice bearing MCF-7 tumors of different sizes. Six months of TAM treatment caused no increase in tumor size (compared to placebo treatment) for animals treated initially following implantation of tumor pieces (approximately 1 mm3) or for animals with 0.2-2 cm2 tumors (growth with 1 month of estrogen treatment). Tumors could be regrown with estradiol treatment in animals treated with either therapy and these tumors contained both estrogen and progesterone receptors. However, more tumors could be restimulated with estradiol following pretreatment with TAM than with placebo. A third group of animals had larger tumors (grown with 7 weeks of estrogen treatment to a >0.5 cm2 area) before TAM or placebo treatment. These tumors partially regressed after 4 months of TAM or placebo treatment but began to regrow in both groups until the end of the experiment at 8 months. Tumors that grew in both groups were estrogen receptor positive and when retransplanted into athymic animals could grow with estradiol. However, the tumor that grew during TAM therapy, when retransplanted, could grow successfully only with further TAM treatment. Tumors growing with TAM contained double the estrogen receptor content of the estradiol-stimulated MCF-7 tumors that were not exposed to TAM (390 ± 37 fmol/mg protein versus 174 ± 14 fmol/mg protein). These results may represent a form of TAM resistance, i.e., TAM dependence that may occur before hormone independence is exhibited.

70. | 1988 | Article – tamoxifen not anti-estrogenic effect | LOVE RR | Bone-mineral density in women with breast-cancer treated with adjuvant tamoxifen for at least 2 years | While in limited animal studies tamoxifen is reported to protect against loss of bone mineral, data in humans are lacking. We measured bone mineral density (BMD) using single photon absorptiometry at the radius and dual photon absorptiometry at the lumbar spine in breast cancer patients treated with chemotherapy at our institution. In this group, 37 women were not treated with tamoxifen (NT) and 48 women were treated with tamoxifen (T) for at least two years. Younger age, greater weight and height, premenopausal status, and shorter time since menopause were found to be significant predictors of greater BMD. Tamoxifen-treated women had been postmenopausal for more years (p = 0.012). Regression analyses used to adjust for differences in risk of bone loss did not reveal significant differences in BMD between the two groups of women. For the postmenopausal women (27 NT and 34 T subjects), the adjusted mean BMD (g/cm2) at the spine was 1.11 (NT), 1.11 (T) (p = 0.93); and at the radius 0.63 (NT), 0.62 (T) (p = 0.30). This limited retrospective study suggests that tamoxifen does not have anti-estrogenic effects on BMD.

71. | 1984 | Non-steroidal antiestrogens - receptor-binding and biological response in rat uterus, rat mammary-carcinoma and human-breast cancer-cells | WAKELING AE | No abstract available from any of the data bases at any of the institutions in addition to all relevant free databases.

72. | 1983 | Discrete sequential boundaries for clinical-trials | LAN KKG | Pocock (1977), O'Brien & Fleming (1979) and Slud & Wei (1982) have proposed different methods to construct discrete sequential boundaries for clinical trials. These methods require that the total number of decision times be specified in advance. In the present paper, we propose a more flexible way to construct discrete sequential boundaries. The method is based on the choice of a function, \( q_*(t) \), which characterizes the rate at which the error level \( q \) is spent. The boundary at a decision time is determined by \( q_*(t) \), and by past and current decision times, but does not depend on the future decision times or the total number of decision times.