Cost-Effectiveness Analysis of Exemestane Compared with Megestrol in Patients with Advanced Breast Carcinoma

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BACKGROUND. The objective of this study was to determine the potential economic implications resulting from using exemestane (EXE), a new steroidal, irreversible aromatase inactivator, compared with megestrol acetate (MA) in patients with advanced breast carcinoma.

METHODS. The model used the clinical results from the manufacturer-sponsored, international, randomized, controlled, double-blind trial of patients with postmenopausal, tamoxifen-refractory advanced breast carcinoma. Seven hundred sixty-nine women were randomized to EXE 25 mg per day or MA 40 mg four times daily EXE was well tolerated, significantly delayed tumor progression (relative risk [RR], 0.82; 95% confidence interval [95% CI], 0.70–0.97), and prolonged survival (RR, 0.77; 95% CI, 0.59–0.99). Lifetime effectiveness projections were made using the trial efficacy results to the U.S. market using a 1000-day (≈3-year) time frame. Because the median survival of patients who received EXE was not reached, it was projected from the Cox model. There were no differences in the rate of hospitalization. The average wholesale prices for EXE and MA were used.

RESULTS. Patients who received EXE were projected to have a mean survival benefit of 53.5 days (estimated 95% CI, 2–100 days) and to incur at an additional cost of $1559 per patient (estimated 95% CI, $880–2075). The incremental cost effectiveness (CE) ratio using EXE was $10,600 per life year gained (estimated 95% CI, $6200–209,000). If MA had no costs, then the CE ratio increased to $12,200 per life year. Using a 5-year projection, the CE ratio for EXE was $5900 per life year. The projected survival at 1000 days was 53.9% in the EXE cohort compared with 44.8% in the MA cohort.

CONCLUSIONS. EXE, compared with MA, is projected to increase survival at a modest added cost. If treatment with EXE delays or defers initiating more costly therapies, then it may even be cost saving. ***Cancer* 2001;91:484–9.**
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The type, timing, and sequencing of hormonal therapy for patients with breast carcinoma constitute one of the most extensively studied areas in contemporary oncology. In postmenopausal women, estrogen synthesis occurs primarily by adrenal gland conversion of androgens by aromatase enzymes.[1] Two types of compounds inhibit or block the aromatase-mediated conversion of androgens to estrogens: nonsteroidal aromatase inhibitors (aminoglutethimide, letrozole, and anastrozole) and steroidal aromatase inactivators. The latter compounds are termed *aromatase inactivators*, because they bind to the aromatase enzyme irreversibly, thus permanently inactivating it.

Single-agent hormone therapy is the treatment of choice for

many women with metastatic breast carcinoma: primarily those with known estrogen receptor positive tumors, a relatively indolent pace of disease, and no or modest liver involvement.[2] Tamoxifen has been the long-standing initial hormonal therapy for such patients. For second-line therapy or for failure during adjuvant tamoxifen treatment, megestrol acetate (MA), a progestional agent, has been used most commonly but is only modestly effective and is associated with frequent adverse effects. Recent randomized trials have shown that the nonsteroidal aromatase inhibitors (letrozole and anastrozole) provide an alternative to MA as second-line therapy.[3–5]

Exemestane (EXE), a steroidal aromatase inactivator, has been compared with MA in a large, international, double-blind trial in postmenopausal women with tamoxifen-refractory, advanced breast carcinoma. The recently published results showed that EXE was well tolerated and significantly delayed tumor progression and time to treatment failure with a significantly longer median survival time (median not reached) compared with MA.[6] Because new drugs commonly have greater costs than those that they are superseding, an economic projection is important prior to their inclusion on formularies. In this report, we project the incremental cost effectiveness of EXE compared with MA and make inferences about this entire class of medications as treatment after following antiestrogen therapy in patients with advanced breast carcinoma.

TABLE 1
Selected Results and Observations from the Exemestane-018 Trial

Variable	EXE (n = 366 patients)	MA (n = 403 patients)
Deaths as % of initial cohort	28	32
Treatment (weeks)		
Mean	30.4	25.4
Median	17.0	16.6
Treatment stopped due to adverse events (%)	1.7	5.0
Objective response (%)		
CR	2.2	1.2
PR	12.8	11.2
SD	40.7	41.9
Median time to tumor progression, weeks	20.3 (16.1–24.7)	16.6 (15.6–22.9)
Time to tumor progression risk ratio (range)	0.82 (0.70–0.97)	—
Median time to treatment failure (weeks)	16.3 (15.4–21.1)	15.7 (13.7–16.7)
Survival (weeks)		
Median	Not reached	123.4
95% CI	(122.1–I)	(99.6–I)
Survival		
at 1 year	0.82	0.75
at 2 years	0.60	0.54
Survival risk ratio (range)	0.77 (0.59–0.99)	—
Duration of response (months)		
6	0.96	0.85
12	0.67	0.59
Hospitalization		
Any time on protocol (%)	23.2	25.5
Mean hospital days per patient	2.29	2.53
Median time from entry to first hospital (days)	81	56
Treatment days (mean)	213	178

Exe: exemestane; MA: megestrol acetate; CR: complete response; PR: partial response; SD: stable disease; 95% CI: 95% confidence interval; I: indeterminate.

MATERIALS AND METHODS

Review of EXE 018 Trial

Trial 018 was a multicenter, international, double-blind, Phase III, randomized, controlled trial the details of which have been reported elsewhere.[6] This was the key trial performed with the intent of supporting the registration of EXE in the metastatic setting. The trial enrolled 769 women with advanced breast carcinoma who had failed tamoxifen either as adjuvant therapy or as first-line therapy for metastatic disease. Patients were randomized to either EXE (Aromasin; Pharmacia & Upjohn, Milan, Italy) 25 mg per day (366 patients) or MA (Megace; Bristol-Myers Squibb, Princeton, NJ) 40 mg four times daily (403 patients). Treatment was continued until evidence of disease progression. The trial's primary efficacy endpoint was a comparison of the objective response rates. Independent reviews of data were performed for patients with responsive disease and blinded to treatment. Secondary endpoints were duration of response, time to disease progression, time to treatment failure, and survival. A sample size of 750 patients was calculated to be adequate for testing the hypothesis of equivalence between treatments in the objective response rate with a power of 80% (α, 0.10; one sided).

Patient characteristics were similar to those participating in other trials for this condition. All characteristics were balanced between treatment groups: The median age was 65 years, about 66% of the women had received prior hormonal therapy for advanced breast carcinoma, and about 33% of the women had unknown estrogen receptor status. The Eastern Cooperative Oncology Group performance status distribution was 45% level 0, 45% level 1, and 10% level 2. Other characteristics suggested that these cohorts had a greater tumor burden than other recent studies: 57–59% had visceral disease, only 31% had bone or skin only involvement, and approximately 80% had measurable disease.

The clinical results are listed in Table 1. The median time to tumor progression was significantly longer in the EXE cohort at 20.3 weeks compared with 16.6 weeks in the MA cohort ($P = 0.037$; log rank test).

A quality-of-life assessment was performed using

the European Organization for Research and Treatment of Cancer QLQ C-30 questionnaire. Although statistically significant differences in specific subscales were seen in the EXE cohort compared with the MA cohort, no differences were seen in the aggregate global health score between prior to disease progression. Therefore, this analysis does not include a quality-of-life adjustment for the differences in survival.

Financial or resource use was not measured directly in the trial or after disease progression. However, the hospitalization and adverse events were collected (source: Final Report, Pharmacia-Upjohn). About 25% of patients were hospitalized while on trial. A nonsignificant difference in the average number of hospital days of less than 1 day was seen between cohorts. The toxicity profile showed few Grade 3 or 4 adverse events in either group. The use of concomitant medications did not differ between groups. Adverse drug events lead to the discontinuation of therapy in 1.7% of the EXE patients and in 5.0% of the MA patients.

Methods and Assumptions of Cost-Effectiveness Projection

This analysis is a secondary analysis that uses the currently available results assessed after a preplanned number of events (tumor progression). For this economic analysis, the primary endpoint was overall survival. The median survival has not been reached for EXE cohort and was 123.4 weeks in the MA cohort ($P < 0.039$). At the time of evaluation, 28–32% of the patients in the original cohorts had died. At 1 year and 2 years from randomization, the EXE cohort had greater survival percentage at 82% compared with 75% and at 60% compared with 54%, respectively (data were abstracted from survival curves; *P* values were not determined).

This assessment makes an effectiveness projection using the trial efficacy results. This analysis was performed using United States drug costs and a societal perspective to estimate the incremental cost effectiveness of EXE. Because the model primarily uses direct drug costs and survival, the costs of EXE and MA in any local market can be inserted. The assessment makes the following assumptions in addition to the trial entry criteria. 1) Only survival was considered: No quality-of-life adjustments were made. 2) Costs, quality of life, and survival after the development of progressive disease were assumed to be the same independent of initial therapy and, thus, were not considered. 3) Protocol specific costs due to radiologic imaging and laboratory tests were excluded. 4) There was no difference in hospital resource use for breast carcinoma specific or treatment-related adverse events. 5) The daily hazard rate for death was constant over time. 6) Projections estimating the 2.5% CI and the 97.5% CI of costs and survival assume that the distribution of events or risks in the EXE cohort and the MA cohort have the same shape and variance.

The primary costs were the daily costs for EXE and MA. Costs were based on their current average wholesale price. In sensitivity analyses, a range of costs was assessed. Because the EXE cohort had a prolongation in survival, their total costs may include additional health care expenses beyond daily drug costs. 7) The additional costs were projected at $150 per each 28 days of added survival: a physician outpatient visit with a detailed history, a detailed physical examination, and moderate complexity decision making (common procedural terminology 99214); a complete blood count; chemistries; and a half-day of lost wages for family or companion.

The baseline estimate for the average number of treatment days was taken directly from the trial results. An estimate of the 95% CI around the median time to disease progression was made and was used in the sensitivity analysis.

Modeling the benefit of therapy

For economic analyses, the change in the mean rather than median survival is the most important endpoint.[8,9] Any estimation of the mean survival depends on the duration of follow-up and on the proportion of censored observations in any given time frame. The model used a 1000-day (an ≈2.75-year) baseline time frame. A 5-year projection was evaluated in a sensitivity analysis.

The observed median survival for the MA cohort was used to estimate the daily hazard rate of death in the cohort.[10] For the EXE cohort, the daily hazard rate of death was estimated by multiplying the observed relative risk for the EXE cohort by the daily risk for the MA cohort. For example, the median survival in the MA cohort of 123.4 weeks translates to a daily hazard of 8×10^{-4}. Using the EXE relative risk of 0.77, its estimated daily hazard was 6.16×10^{-4}. The 95% CI of the EXE daily hazard was estimated by multiplying the lower and upper limits of the relative risk of the EXE cohort (0.59 and 0.99, respectively) by the daily risk for the MA cohort.

Cost-effectiveness projection

The cost-effectiveness (CE) ratio is calculated as follows, excluding the discounting adjustment: ([cost per day EXE × EXE days used before progression] + reassessment costs every 28 days) − ([cost per day MA × MA days used before progression] + reassessment costs q 28 days)/(survival days EXE − survival days

TABLE 2
Projections of Costs and Efficacy

Variable	EXE	MA	Difference
Costs			
95% CI on treatment (days)	169–259	167–245	−76 to +92
Drug cost per day, AWP ($)	7.13	1.32	5.81
Average total drug costs per patient ($)	1517	235	1,282
95% CI of drug costs per patient ($)	1204–1847	221–324	880–1626
Survival hazard rate			
Daily hazard rate for death	—	0.0008	—
Daily hazard rate at RR of 0.77	0.000616	—	—
Daily hazard rate at RR of 0.99 (2.5% CI)	0.000792	—	—
Daily hazard rate at RR of 0.59 (97.5% CI)	0.000472	—	—
Average survival @ 1,000 days			
Risk ratio, 0.77	746.3	688	+58.3
Lower limit for RR of 0.59 (2.5% CI)	797	—	+109
Upper limit for RR of 0.99 (97.5% CI)	690.4	—	+2.4
Survival at 1000 days (%)			
Baseline	53.9	44.8	+9.1
2.5% RR	62.3	—	+17.5
97.5% RR	45.2	—	+0.4
Median survival (weeks)	160.3	123.4	+36.9
3% Discounting of baseline estimates			
Average treatment costs ($)	1490	231	1,259
Average survival at 1000 days	684.9	631.4	53.5

EXE: exemestane; MA: megestrol acetate; 95% CI: 95% confidence interval; RR: risk ratio.

TABLE 3
Cost-Effectiveness Analysis Project

Variable[a]	Baseline	95% CI range
Mean survival benefit at 1000 days (days)	53.5	2.2–100.0
Baseline		
Exemestane vs. megestrol treatment (days)	35	35
Additional drug costs per patient ($)	1259	1259
Additional treatment monitoring costs ($)	300	0–450
Total additional treatment costs ($)	1559	1259–1709
Incremental cost per life yr ($/yr)	10,600	209,000–6200
Lowest cost difference case scenario (lower 2.5% estimate of CI)		
Exemestane vs. megestrol treatment (days)	92	92
Total additional costs per patient ($)	1926	1625–2075
Incremental cost per life yr ($/yr)	13,100	344,600–6000
Greatest cost difference case scenario (upper 97.5% estimate of CI limit)		
Exemestane vs. megestrol treatment (days)	−76	−76
Total additional costs per patient ($)	1,180	880–1300
Incremental cost per life year ($/yr)	8,000	220,500–3200

95% CI: 95% confidence interval.
[a] Drug costs and survival are discounted at 3%.

MA). The 95% CI for treatment days was estimated from the observed mean duration of treatment and the 95% confidence interval around the time to progression using the following formula: (2.5% or 97.5% CI of days to progression/median days to progression) × (mean days of treatment). The extremes of the range in the difference in treatment days was calculated as follows: (greatest number of EXE days − fewest number of MA days) and (fewest number of EXE days − greatest number of MA days).

In an attempt to make these reports easily convertible to other settings or set of assumptions, only the final CE ratios included a 3% discounting. Sensitivity analyses included 0% and 5% discount rates.

RESULTS

Table 2 lists the key observed results, the cost projections, and the survival projections relevant to the economic analysis. Because patients in the EXE cohort were on treatment 35 days longer, EXE is projected to have a $5.81 greater daily cost. The total drug cost difference was $1283 per patient without discounting and $1259 after 3% discounting.

Using the hazard rate of 0.77 for EXE, the average survival of the EXE cohort would be 58.3 days longer than that of the MA cohort (746 days vs. 688 days) during the 1000-day evaluation period. After 3% discounting of future benefits, the difference decreased to 53.5 days. The relative survival percentage at 1000 days was projected to increase by about 9% in the EXE cohort (53.9% vs. 44.8%). The median survival for the EXE cohort was projected to increase by 36.9 weeks (160.3 weeks vs. 123.4 weeks).

Using the 95% CI of the relative risk of death with EXE, the projected extremes of the survival advantage ranged from 2.4 days to 109 days. The projected increase in 1000-day survival changed from 0.4% to 17.5%.

Table 3 shows the CE projections. The primary results using EXE observed additional days of treatment, inferred costs of additional follow-up, and the baseline reduction in relative risk of death also are shown. The estimate of the 95% CI in efficacy is shown as a column, and the estimates for costs are shown in rows. The baseline CE ratio is $10,600 per year of life gained with EXE compared with MA.

Sensitivity Analysis

A variety of changes in assumptions of costs and efficacy were assessed in "what if" or sensitivity analyses. If the added costs for health care visits associated with prolonged survival are excluded, then the CE ratio decreases to $8590 per life year. Discounting has only a modest effect on the results. Using alternative annual discount rates of 0% and 5%, the baseline CE ratio decreased slightly to $9900 (95% CI, $5800–195,000) per

life year with no discounting and increased slightly to $11,200 at 5% discounting. The increasing CE ratio at a higher discount rate suggests that most of the future costs are close to the present time and that the discounted gain in life years is the primary driver in increasing the CE ratio.

The CE ratio was much more sensitive to changes in the efficacy projections than the cost projections. Using the 95% CI of EXE's efficacy and the baseline cost, the CE ratio ranged from $6200 to $209,000 per life year gained. The estimated 95% CI or range of costs reflects the differences in treatment days between EXE and MA. Using the baseline efficacy estimate, the CE ratio for EXE ranged from $8050 to $13,100 per life year gained.

Using the baseline efficacy estimate, if MA cost nothing, then the CE ratio of using EXE would increase to $12,200 per life year gained. Using the commonly cited $50,000 per life year threshold, EXE would have to cost $34 per day. If the number of additional treatment days with EXE were increased to be equal to the projected survival advantage (i.e., from 35 days to 58 days), then the CE ratio would increase to $11,700 per life year. If the daily risk of death and the relative benefit from EXE persist for up to 5 years, the CE ratio would decrease to $5900 per life year.

DISCUSSION

EXE is the first oral steroidal aromatase inactivator that has been found to be active in women with advanced breast carcinoma. This report builds on the results of the recently completed double-blind comparison of EXE with MA, which was the prior standard of care, as treatment for advanced breast carcinoma in women with previously hormonally responsive disease. EXE was found to provide an additional benefit at a very modest additional cost.[11,12]

The benefit from EXE appears to be principally due to increasing the duration of response in responding patients. Most patients during the trial were not hospitalized. After disease progression, no major differences between the two arms were seen in the first type of subsequent therapy if any was given. This highlights one of the limitations of the analysis: the modest number of adverse events (deaths) for the primary endpoint of the economic analysis. However, although it is unlikely that EXE changed the site and symptoms associated with tumor progression, subsequent physician treatment patterns may be altered. A small relative delay or deferral in using systemic chemotherapy would affect the CE projections, such that EXE actually could be cost saving compared with MA. If even one dose of taxotere or paclitaxel or one course of capecitibine were avoided, EXE would be cost saving.

Since the initiation of the EXE trial, anastrozole and letrozole have been approved for use in patients with advanced breast carcinoma after disease progression on antiestrogen therapy based on clinical trials also using MA as the comparator.[3–5] Although EXE belongs to a different class of molecules, a steroidal aromatase inhibitor (rather than a nonsteroidal aromatase inhibitor) and an inactivator (rather than an inhibitor), the similarities in the clinical setting and design of these trials may encourage clinicians and pharmacists to compare the agents directly.

EXE was the only agent that showed statistically significant differences ($P < 0.05$) in the time to treatment failure, time to tumor progression, and survival. The median time to progression differed between agents by about 0.5 months. The adverse effect profile showed that EXE and anastrozole were discontinued slightly less often than letrozole. No striking differences in weight gain, venous thrombosis, vaginal bleeding, or hot flashes were seen. Although the patients in the EXE study appear to have been a cohort with a poorer prognosis, the 2-year survival rate in the control group of patients who received MA was the same or greater than that in the intervention arms in the anastrozole and letrozole study.

Many clinical and health service researchers have found that a three 3-benefit in survival is a useful threshold for a meaningful benefit for a new therapy. Anastrozole (4.2 months) and letrozole (3.8 months) exceed this threshold. Because the median survival has not been reached for the EXE study, only projections are possible. This model projects an increase in the median survival of 8.5 months. If it is confirmed, then this will be the most important clinically differentiating result between these agents.

Additional indirect evidence supporting EXE as the optimal aromatase therapy is the evidence for its use in patients with tumors that have failed therapy with tamoxifen and MA[13] or with tamoxifen and nonsteroidal aromatase inhibitors.[14] In each of those Phase II studies involving 91 women and 241 women, respectively, about 25% of patients had a response or had stable disease for at least 6 months.

Although this analysis focused on EXE, given the similar per unit costs of anastrozole and letrozole compared with MA, these agents also are likely to have low incremental CE ratios. Drummond projected that anastrozole, compared with MA, had an incremental cost of about ≈£3739 (≈$6180) per life year gained based on the United Kingdom National Health Service drug prices when including treatment provided during the added period of survival.[15]

Clearly, a direct comparative trial between steroidal and nonsteroidal aromatase inhibitors to determine the optimal agent would be valuable. Unfortunately, a review of the National Cancer Institute's Cancer Net web site shows no active clinical trials. All current efforts with these agents are in either an adjuvant or first-line metastatic setting with tamoxifen as the control agent or entail the evaluation of new antiestrogens.

Given the very favorable clinical and economic features of EXE and this general class of medications, a global concern is whether they are being underutilized in North America and Europe. Designing a treatment program for patients with metastatic breast carcinoma entails balancing acceptable risks, side effects, and activity. Treatment algorithms for metastatic breast carcinoma advise that patients with extensive visceral involvement be treated with intravenous chemotherapy. However, the definition of extent of visceral involvement is subject to interpretation. In this trial, over 50% of patients had visceral disease as their primary metastatic site. An unmeasurable barrier in the United States is a common impression that hormonal therapy is not active therapy, because initial complete or partial responses are infrequent. Finally, because these medications are taken orally in the United States, Medicare does not cover their costs. Given the financial incentives in current American oncology care to give intravenous chemotherapy, all of these reasons may lead to underuse. In conclusion, the potential risks and costs of EXE 25 mg per day are low for postmenopausal women with hormonally responsive breast carcinoma who fail to respond to chemotherapy with tamoxifen: For these patients, EXE has minimal risks and may provide substantial benefits at a very modest cost.

REFERENCES

1. Lonning PE. Pharmacological profiles of exemestane and formestane, steroidal aromatase inhibitors used for treatment of postmenopausal breast cancer. *Breast Cancer Res Treat* 1998;49(Suppl 1):S45–52.
2. Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med* 1998;339:1609–18.
3. Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two Phase III trials. Arimidex Study Group. *J Clin Oncol* 1996;14:2000–11.
4. Buzdar AU, Jonat W, Howell A, Jones SE, Blomqvist CP, Vogel CL, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature Phase III trials. Arimidex Study Group. *Cancer* 1998;83:1142–52.
5. Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate [see comments]. *J Clin Oncol* 1998;16:453–61.
6. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a Phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol* 2000; 18:1399–411.
7. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996.
8. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;113:147–54.
9. Etzioni R, Urban N, Baker M. Estimating the costs attributable to a disease with application to ovarian cancer. *J Clin Epidemiol* 1996;49:95–103.
10. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, et al. Modelling in economic evaluation: an unavoidable fact of life [editorial]. *Health Econ* 1997;6:217–27.
11. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992;146:473–81.
12. Smith TJ, Hillner BE, Desch CE. Efficacy and cost-effectiveness of cancer treatment: rational allocation of resources based on decision analysis. *J Natl Cancer Inst* 1993;85:1460–74.
13. Jones S, Vogel C, Arkhipov A, Fehrenbacher L, Eisenberg P, Cooper B, et al. Multicenter, Phase II trial of exemestane as third-line hormonal therapy of postmenopausal women with metastatic breast cancer. Aromasin Study Group. *J Clin Oncol* 1999;17:3418–25.
14. Lonning PE, Bajetta E, Murray R, Tubiana-Hulin M, Eisenberg PD, Mickiewicz E, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a Phase II trial. *J Clin Oncol* 2000;18:2234–44.
15. Drummond M, Thompson E, Howell A, Jonat W, Buzdar A, Brown J. Cost-effectiveness implications of increased survival with anastrozole in the treatment of advanced breast cancer. *J Med Econ* 1999;2:33–43.