

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
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STATISTICAL REVIEWS

Statistical Review and Evaluation

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1 BACKGROUND

This supplemental NDA is comprised of 2 pivotal Phase III trials: 1033IL/0027 and 1033IL/0030, where Trial 1033IL/0027 was conducted in 83 world-wide centers and Trial 1033IL/0030 was conducted in 97 North American centers. Additional trials include Trial 1033NY/0001, an uncontrolled trial, Trial 1033IL/0032, a trial designed to evaluate the effect of anastrozole on peripheral and tumor aromatase activity in early stage breast cancer, Trials A-15-12, 1033IL/0035, 1033IL/0033, clinical pharmacology trials,

This statistical review will only focus on studies 1033IL/0027 and 1033IL/0030.

2 TRIAL 1033IL/0027

2.1 TITLE

A Randomized, double blind, double dummy trial to compare the efficacy and safety of ARIMIDEX™ (ZD1033 1 mg daily) with tamoxifen (20 mg daily) as first line therapy for advanced breast cancer in postmenopausal women.

2.2 DESCRIPTION OF TRIAL 1033IL/0027

2.2.1 Objective

The objective of this study was to compare the efficacy and tolerability of anastrozole (1mg od) with tamoxifen (20mg od) as first line therapy for advanced breast cancer in postmenopausal women.

2.2.2 Design

Trial 1033IL/0027 was a randomized, double blind, double dummy, Phase III study comparing two arms:

- (a) anastrozole (1mg orally od) plus tamoxifen placebo
- (b) tamoxifen (20mg orally od) plus anastrozole placebo

for the first line therapy of advanced breast cancer in postmenopausal women. A separate randomization scheme, incorporating 2 levels of stratification (soft tissue and/or lung disease only vs. all other disease combinations) was prepared for each center by the sponsor. Patients were allocated to treatment in balanced blocks.

Therapy was initiated on the date of randomization (Visit 1). Patients were treated until evidence of objective progression of disease. Patients were reviewed for safety and efficacy at 4-week intervals up to 24 weeks and every 12 weeks thereafter. Assessments continued until objective progression of disease was assigned irrespective of whether trial therapy had been withdrawn prior to progression. After progression patients were reviewed at 6-month intervals until death.

The first patient was recruited on August 21, 1995 and the last patient on July 1, 1998. Data were cut off on March 10, 1999.

2.2.3 Patient Population (Protocol)

The protocol specified a sample size of 660 eligible and evaluable patients with 330 randomized into each treatment arm. The sample size was based on the two primary endpoints: time to disease progression (TTP) and objective response rate. The trial was powered to demonstrate non-inferiority, as defined by the confidence limit, for each of these endpoints. The assumptions made to compute the sample size based on the endpoint of TTP were: (1) the median progression time of 7.7 months for tamoxifen treated patients and of 6.2 months for anastrozole treated patients, (2) a minimum follow-up period of 6 months, (3) an 80% power and a one-sided 5% significance level test. This led to a sample size of 660 patients. The assumptions made to compute the sample size based on objective response rate were: (1) the response rate of 30% for tamoxifen treated patients and 10% reduction for anastrozole treated patients, (2) an 80% power and a one-sided 5% significance level test. This led to a sample size of 502 patients. Since TTP was more demanding in terms of sample size. The trial aimed to recruit 660 patients.

2.2.4 Efficacy Endpoints

The primary efficacy endpoints were time to progression (TTP) and objective response rate. TTP was measured from the randomization date to the date of disease progression or death from any cause. Responders were those patients with a best objective response of complete response (CR) or partial response (PR). In Section 2.8.2, Vol. 6.18 of the NDA submission the sponsor states the following: *"The primary objective of this trial was achieved if the non-inferiority of anastrozole to tamoxifen was obtained on both time to progression and objective-response rate."* Therefore, no multiplicity adjustment for the two primary endpoints was made.

The secondary efficacy endpoints included time to treatment failure, time to death, duration of response, duration of clinical benefit, and health economics. Time to treatment failure was defined as the time from the randomization date to the date of disease progression or withdrawal of study treatment for any reason, including death from any cause. Time to death was defined as the time from the randomization date to the date of death. Duration of response was defined only for responding patients. It was defined as the time from the randomization date to the date of first observed progression or death from any cause; and from the date of first documentation of response to the date of first observed progression or death from any cause. Duration of clinical benefit was measured for patients with clinical benefit. It was defined from the randomization date to the date of first observed progression or death from any cause. Health economic variables were the number of patients who receive radiotherapy, chemotherapy, or hormonal therapy following the withdrawal of trial treatment, and the number of patients who had any overnight hospitalizations for reasons related to breast cancer following the withdrawal of trial treatment.

2.2.5 Interim Analysis

An interim analysis was carried out to demonstrate early indication of efficacy in patients with soft tissue and/or lung disease stratum. The response rate between the two treatment groups was compared using logistic regression. The purpose of this analysis was to give an early indication of response rates that may be achieved by anastrozole in this group of patients. The information was required for administrative reasons. Because the interim analysis had no effect on the trial blinding and there was no formal analysis of the interim data, no statistical adjustments were made to the final analysis of objective response rate.

2.2.6 Statistical Methods (Protocol)

This section summarizes the statistical methods specified in the protocol.

A Cox regression model will be used to assess equivalence of the treatment groups in the population of all patients randomized for time to progression, time to treatment failure and time to death. If the median time to death cannot be estimated at the time of submission, only Kaplan-Meier curves will be presented for each treatment group. The following covariates will be included in the model: age (≤ 65 yrs, > 65 yrs), previous hormonal therapy (yes, no), oestrogen and progesterone receptor status at diagnosis (ER status is positive or PR status is positive or both ER and PR are positive versus others), and site of disease at entry (soft tissue alone, lung disease alone, soft tissue and lung disease vs. other sites or combinations of sites). The treatment comparison will be estimated with a hazard ratio along with the lower one-sided 95% confidence limit for the hazard ratio. The assumption of the Cox regression model will be assessed using plots of the log of the survivor function. If there is a departure from the assumptions, the analysis will be carried out using a suitable non-parametric test (e.g. log-rank test). Additionally, these analyses will be repeated including terms for the interaction between treatment and each covariate. This will be done by globally including all interaction terms and assessing the change in likelihood.

Objective response rate will be compared between treatment groups using logistic regression with the four factors specified as above. The comparison will be estimated using the odds ratio together with the lower one-sided 95% confidence limit for the odds ratio.

The health economic variables will be summarized by trial treatment actually received and by trial visit. This will summarize any trial differences over time.

Statistical analyses for all efficacy endpoints will be performed on the intent-to-treat (ITT) population, which is considered as the primary analysis. Analyses for endpoints of time to progression, objective response rate, and time to death (survival) will also be performed on the per-protocol population, which is considered as the secondary analysis.

2.3 SPONSOR'S RESULTS AND REVIEWER'S COMMENTS

All 668 randomized patients were included in the primary (ITT) analysis for all efficacy endpoints. A total of 87 (13.0%) patients had significant protocol violations or deviations, or both. Of these, 50 patients were randomized to anastrozole and 37 patients to tamoxifen. After excluding the 87 patients, a total of 581 (87.0%) patients were included in the secondary (per-protocol) analysis.

The sponsor's results of patients' baseline characteristics and of efficacy endpoints are summarized in the subsequent sections. This reviewer's comments will be included as needed.

2.3.1 Baseline Characteristics

A total of 668 female patients were randomized to trial treatment, of which 340 patients were randomized to anastrozole and 328 to tamoxifen. Table 1 summarizes the sponsor's results of demographic details for age, height, weight, BMI, and ethnic origin for all patients at entry. The results showed that demographic characteristics in the two treatment groups were similar to each other.

Table 1: Sponsor's demographic characteristics

Demographic characteristic		Treatment group	
		Anastrozole 1 mg [n=340]	Tamoxifen 20 mg [n=328]
Age (years)	Mean	67	66
	SD	11.0	10.6
	≤ 65 [n (%)]	160 (47.1%)	160 (48.8%)
	> 65 [n (%)]	180 (52.9%)	168 (51.2%)
Height (cm)	n (%)	320 (94.1%)	310 (94.5%)
	Mean	159	159
	SD	7.1	7.2
Weight (kg)	n (%)	333 (97.9%)	318 (97.0%)
	Mean	68	68
	SD	13.2	12.9
Body mass index (kg/m ²)	n (%)	317 (93.2%)	308 (93.9%)
	Mean	27	27
	SD	4.9	5.0
Ethnic origin [n (%)]	Caucasian	313 (92.1%)	297 (90.5%)
	Afro-Caribbean	3	1
	Asian/Oriental	0	2
	Hispanic	9	9
	Other ^a	15	19

^a Other includes patients of mixed origin.

2.3.2 Primary Efficacy Endpoints

2.3.2.1 Time to Progression (TTP)

Using the ITT population, a total of 496 patients had disease progression. Of these, 249 patients were randomized to anastrozole and 247 patients to tamoxifen. The estimated median time to progression was 251 days for patients randomized to anastrozole and 252 days for patients randomized to tamoxifen. The sponsor's adjusted analysis (Table 2) showed that the tamoxifen: anastrozole comparison had a hazard ratio very close to 1. (A hazard ratio of 1 indicates that the two treatments were identical in the "instantaneous", or immediate, risk of disease progression.) The lower 1-sided 95% confidence limit for the hazard ratio was 0.86, which was greater than the statistical criterion of 0.80 required to declare non-inferiority. Consistent results were obtained from the unadjusted analysis, which gave a hazard ratio of 1.01 and a lower 95% confidence limit of 0.87. The sponsor's Kaplan-Meier probability plot of time to progression is shown in Figure 1.

Using the PP population (secondary approach), 581 patients were included in this population. Of these, 290 (49.9%) patients were randomized to anastrozole and 291 (50.1%) patients to tamoxifen. A total of 435 (74.9%) patients had disease progression. Of these, 218 patients were randomized to anastrozole and 217 patients to tamoxifen. The estimated median time to

progression was 251 days for patients randomized to anastrozole and 252 days for patients randomized to tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 2).

Table 2: Sponsor's statistical analysis of TTP

Population	Comparison	Hazard ratio ^a	One-sided lower 95% CL
	Tamoxifen: anastrozole		
ITT	Adjusted analysis ^b	0.99	0.86
	Unadjusted analysis ^c	1.01	0.87
PP	Adjusted analysis	0.97	0.83
	Unadjusted analysis	0.98	0.84

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

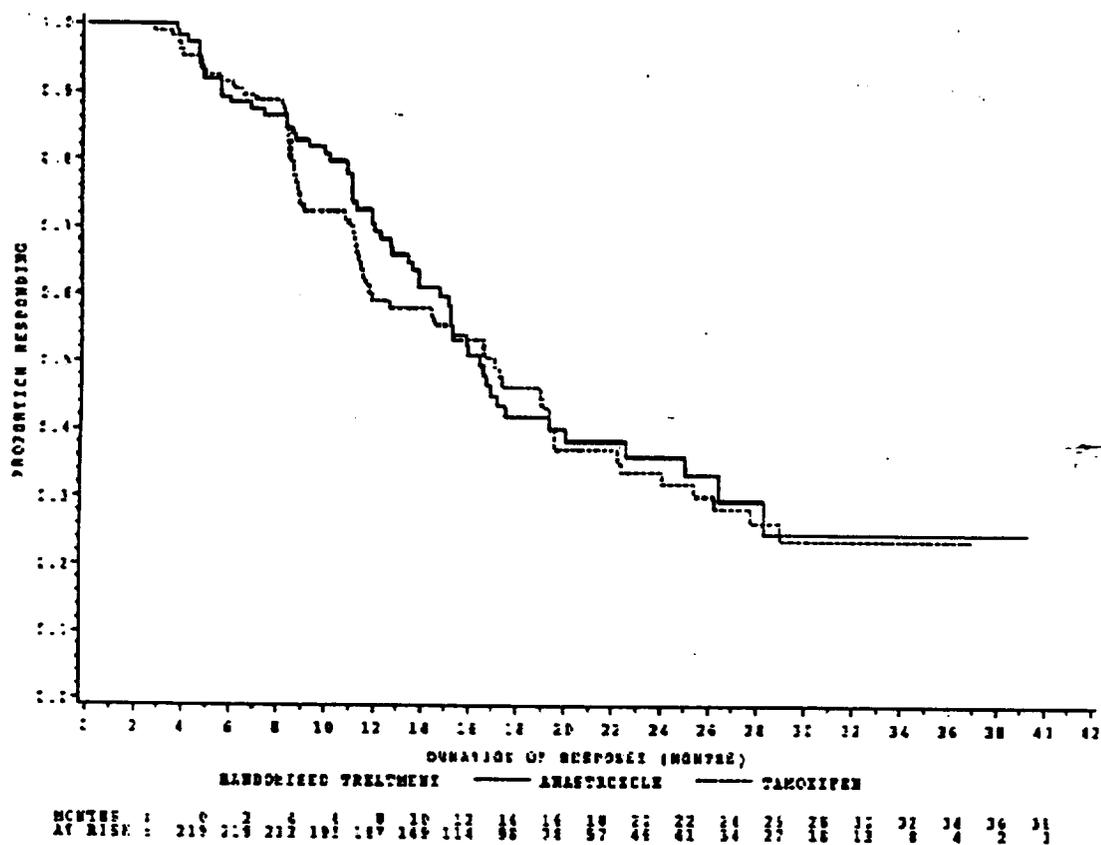
^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

REVIEWER'S COMMENTS:

- The statistical reviewer confirmed the sponsor's results. Both adjusted and unadjusted analyses led to consistent results.
- The medical officer evaluated this endpoint for each patient. The results were very similar to those based on the sponsor's data (see Table 8).
- This reviewer obtained two-sided 95% confidence intervals of the hazard ratio using MO's and Sponsor's data, respectively. The lower limits of the confidence intervals were 0.8 or greater (see Table 8).

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Figure 1: Sponsor's Kaplan-Meier probability of TTP using ITT population



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2.3.2.2 Objective response (CR or PR) Rate

Using the intent-to-treat population, the best objective-response rate of CR or PR was very similar for patients randomized to receive anastrozole and patients randomized to receive tamoxifen (32.9% vs. 32.6%, see Table 3).

Table 3: Sponsor's objective response using ITT population

Objective response	Number (%) of patients	
	Anastrozole 1 mg [n = 340]	Tamoxifen 20 mg [n = 328]
Responders	112 (32.9%)	107 (32.6%)
Complete response	19 (5.6%)	16 (4.9%)
Partial response	93 (27.4%)	91 (27.7%)
Non-responders	228 (67.1%)	221 (67.4%)
Stable disease \geq 24 weeks	79 (23.2%)	75 (22.9%)
Stable disease < 24 weeks	9 (2.6%)	8 (2.4%)
Progression	140 (41.2%)	138 (42.1%)

Table 4 summarizes the sponsor's results of statistical analysis of objective-response rate. Results of the adjusted analysis (using the ITT population) showed that the estimated difference in response rate (-1.01%) favored tamoxifen. The lower 1-sided 95% confidence limit for the difference rate (anastrozole - tamoxifen) was -6.74%, which was greater than the statistical criterion of -10% to declare non-inferiority. The unadjusted analysis gave an estimated difference in response rate of 0.32% and a lower 95% confidence limit of -5.37% which again fell within the statistical criterion for determining non-inferiority. Therefore, the sponsor concluded that anastrozole was equivalent to tamoxifen in terms of objective-response rate.

The sponsor's results from the per-protocol analysis were consistent with those from the ITT analysis. The proportion of patients who had an objective response rate of CR or PR for patients randomized to anastrozole was similar to those randomized to tamoxifen (33.4% vs. 34.7%). The estimated differences in response rates were -2.73% and -1.26% from the adjusted and unadjusted analyses, respectively, which were in favor of tamoxifen. The non-inferiority of anastrozole was demonstrated from the lower 1-sided 95% confidence limit for the difference in response rates, which was greater than the statistical criterion of -10% from both the adjusted (-8.86%) and unadjusted (-7.34%) analyses (see Table 4).

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Table 4: Sponsor's statistical analysis of objective response rate

Population	Logistic regression	Odds ratio ^a	Lower 95% CL	Estimated difference in response rate ^b	Lower 95% CL
Anastrozole : tamoxifen					
ITT	Adjusted analysis ^c	0.95	0.72	-1.01%	-6.74%
	Unadjusted analysis ^d	1.01	0.77	0.32%	-5.37%
PP	Adjusted analysis	0.88	0.66	-2.73%	-8.86%
	Unadjusted analysis	0.95	0.71	-1.26%	-7.34%

^a Odds ratios of greater [less] than 1.00 indicate that anastrozole was associated with a higher [lower] response rate than was tamoxifen.

^b Difference in response ratios of greater [less] than 0 indicate that anastrozole was associated with a higher [lower] response rate than was tamoxifen.

^c The adjusted analysis was performed using a logistic regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^d The unadjusted analysis was performed using a logistic regression model including treatment factor only.

REVIEWER'S COMMENTS:

- The sponsor's primary analysis (adjusted analysis) specified in the protocol was a logistic regression model that included four prognostic factors. The confidence limits of the difference in response rates based on the adjusted analysis are questionable. The reason follows:

There were four dichotomous prognostic factors in addition to the treatment factor. This means that patients, whether randomized to anastrozole or tamoxifen, were classified to any of the sixteen ($=2^4$) possible sets according to the corresponding values of the four prognostic factors. The sponsor assumed a constant difference (anastrozole - tamoxifen) in response rates across all the 16 prognostic sets. This assumption needs to be verified.

The sponsor's approaches are detailed in Appendix (Section 5.1.2).

- The sponsor's secondary analysis (unadjusted analysis) specified in the protocol was a logistic regression model with the treatment factor as the only factor in the model, which was acceptable.
- This reviewer performed a different unadjusted analysis without using a logistic regression model. This analysis was more robust since it required less assumption than the sponsor's unadjusted analysis. The results were consistent with those of the sponsor's unadjusted analysis. The details are described in Section 2.4.1.
- The medical officer re-adjudicated this endpoint for each patient. The outcomes (whether responding or not) were identical to the sponsor's classification.

2.3.3 Secondary Efficacy Endpoints

2.3.3.1 Time to Death (Survival)

The survival data in the original NDA submission was cut off on March 10, 1999. Since the original survival data were premature (75% of the 668 patients were censored), the agency requested the sponsor on July 24, 2000 for an updated survival data. The updated survival data were received on August 8, 2000; the data were cut off on February 23, 2000.

Using the intent-to-treat population, the death rate, as indicated in Table 5, was slightly higher in patients who were randomized to receive anastrozole (26.8%), compared with patients who were randomized to receive tamoxifen (22.6%) at the first time of data cut-off (March 10, 1999). However, the death rates were similar (37.6% vs. 36.3%) between the two groups at the second time of data cut-off (February 23, 2000). The Kaplan-Meier survival curves for both original and updated data are depicted in Figure 2 and Figure 3, respectively. According to the sponsor's discussion in the submission of survival update, the effect of the longer follow-up was illustrated clearly in the Kaplan-Meier plots. With the minimum follow-up of 8 months at the time of the original submission, the curves for anastrozole and tamoxifen were similar up to this 8-month time point; however, there was a degree of divergence beyond this point. With the minimum 20-month follow-up data now available, the curves remained close out to 20 months. The previous appearance of the Kaplan-Meier curves was likely to have been the result of chance events involving a small number of patients."

Table 5: Sponsor's results of number of deaths using ITT population

Data cut-off date	ITT population	
	Anastrozole (N = 340)	Tamoxifen (N = 328)
March 10, 1999	91 (26.8%)	74 (22.6%)
February 23, 2000	128 (37.6%)	119 (36.3%)

The protocol (p. 210 in the sponsor's vol. 6.19) specified that "if the median time to death cannot be estimated at the time of submission only Kaplan-Meier curves will be presented for each treatment group." As a result, the sponsor did not perform a statistical analysis of survival at both times of data cut-off.

Results from the per-protocol analysis were similar to those from the ITT analysis.

REVIEWER'S COMMENTS:

- This reviewer performed a statistical analysis using the original and updated survival data, respectively (see Section 2.4.3). The results showed that there was no statistically significant difference in survival although the estimated hazard ratio was in favor of tamoxifen.

Figure 2: Kaplan-Meier probability of survival time using ITT population – data cut-off as of March 10, 1999

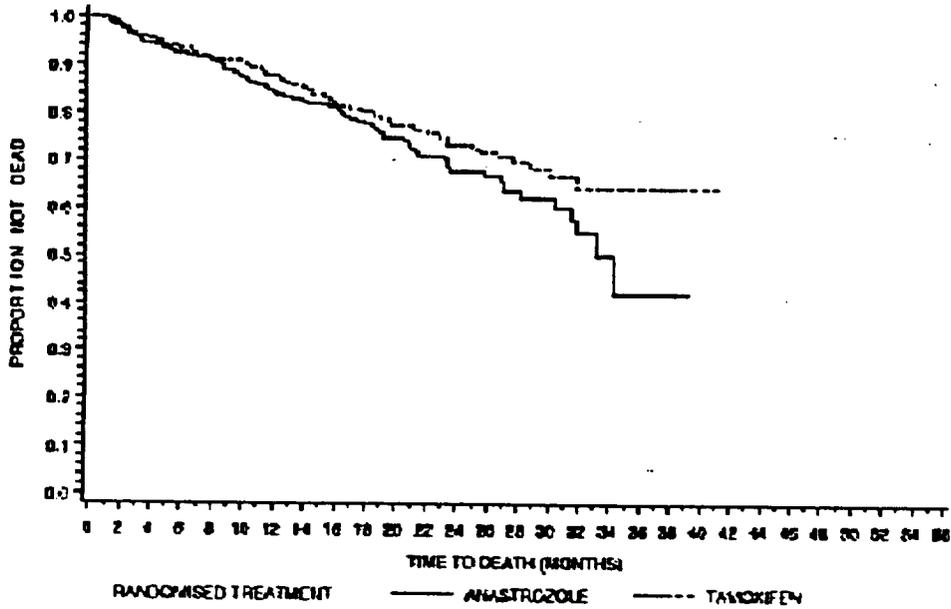
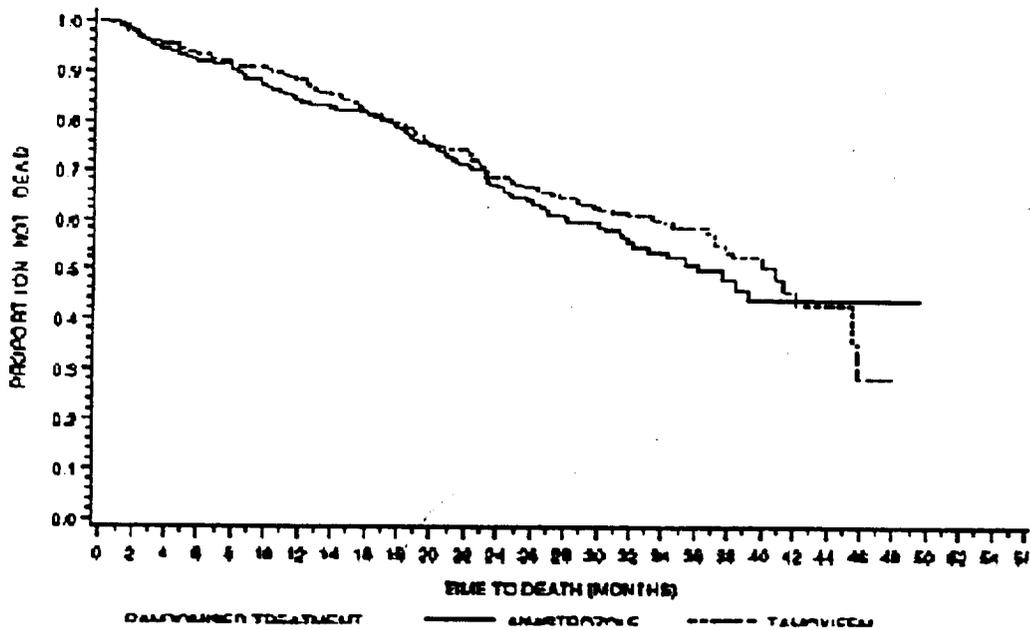


Figure 3: Kaplan-Meier probability of survival time using ITT population – data cut-off as of February 23, 2000



2.3.3.2 Time to Treatment Failure

Of the 668 patients who were randomized to trial treatment, 455 (68.1%) patients had treatment failure resulting from disease progression. 70 (10.5%) patients were withdrawn from the trial for reasons other than disease progression and 8 (1.2%) patients died before progression. This resulted in a total of 533 (79.8%) patients who had treatment failure. A slightly smaller proportion of patients who were randomized to anastrozole (78.5%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (81.1%). Patients who were randomized to anastrozole also had a slightly longer estimated median time to treatment failure (189 days), compared with the time for patients who were randomized to tamoxifen (182 days).

The hazard ratio from the adjusted analysis was very close to 1 and the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen: anastrozole) was 0.89 (see Table 6), which was greater than the minimum value (0.8) required to demonstrate non-inferiority. Similar results were observed from the unadjusted analysis, with a hazard ratio of 1.04 and a lower 1-sided 95% confidence limit of 0.90.

Table 6: Sponsor's statistical analysis of time to treatment failure using ITT population

Comparison	Hazard ratio ^a	Lower 95% CL
Tamoxifen: anastrozole		
Adjusted analysis ^b	1.03	0.89
Unadjusted analysis ^c	1.04	0.90

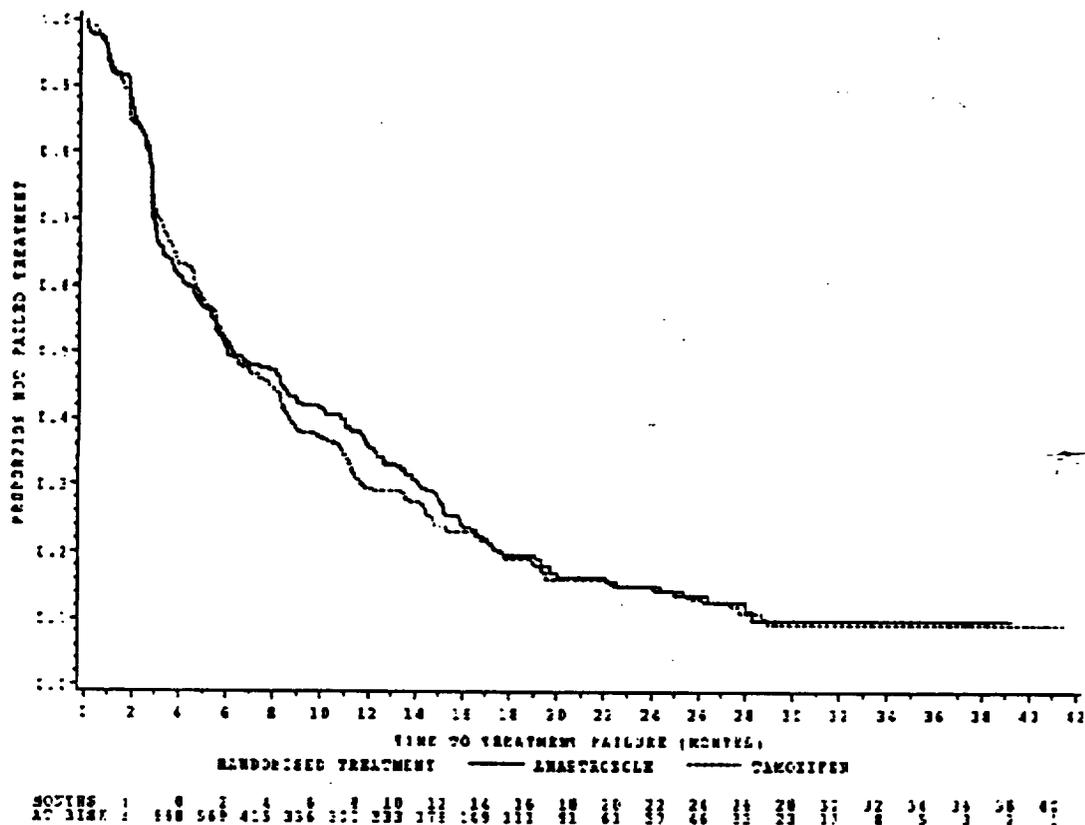
^a Hazard ratios of greater than 1.00 indicate that anastrozole was associated with a longer time to death than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

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Figure 4: Sponsor's Kaplan-Meier probability of time to treatment failure using ITT population



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2.3.3.3 Duration of Response

Duration of response was assessed in responders only (patients who had an objective response of CR or PR) in 2 ways:

- from the date of randomization to the date of first determined progression or death from any cause, and
- from the date of first documentation of response to the date of first determined progression or death from any cause.

Overall, 219/668 (32.8%) patients were considered to be responders. Of these, 112 responders were randomized to anastrozole and 107 responders were randomized to tamoxifen. The estimated Kaplan-Meier median duration of response from the date of randomization was 498 days (duration range from 111 to 1194 days) for responders randomized to anastrozole. The estimated Kaplan-Meier median duration of response from the date of randomization was 518 days (duration range from 83 to 1124 days) for responders randomized to tamoxifen. The estimated Kaplan-Meier median duration of response from the date of first documentation of response was 378 days (duration range from 35 to 1027 days) for responders randomized to anastrozole. The estimated Kaplan-Meier median duration of response from the date of first documentation was 421 days (duration range from 56 to 1037 days) for responders randomized to tamoxifen.

REVIEWER'S COMMENTS:

- The durations of response between the two groups should not be compared because the two respective responder subgroups were treatment-outcome dependent. For labeling purpose, the duration of response should be reported only for the specific treatment under consideration along with the response rate.

2.3.3.4 Duration of Clinical Benefit

Duration of clinical benefit was assessed in patients who experienced clinical benefit, defined as patients who had CR, PR, or SD \geq 24 weeks.

A total of 373 (55.8%) patients demonstrated clinical benefit. Of these, 191 patients were randomized to anastrozole and 182 patients were randomized to tamoxifen. The estimated median duration of clinical benefit was 462 days (duration range from 111 to 1194 days) for those who experienced clinical benefit and were randomized to anastrozole, and 448 days (duration range from 83 to 1260 days) for those who experience clinical benefit and were randomized to tamoxifen.

REVIEWER'S COMMENTS:

- See Reviewer's comments in Section 2.3.3.3.

2.3.3.5 Health Economics

Table 7 summarizes the sponsor's results of the number of patients who were given therapies or who required hospitalization or outpatient visit following the withdrawal of trial treatment. This table presents treatment given to the 476 patients who had withdrawn from the trial by the time of data cut-off. The proportion of patients who were given radiotherapy, chemotherapy, or other therapy following withdrawal from treatment was similar in both treatment groups. A greater proportion of patients who were given tamoxifen received subsequent hormonal therapy.

Table 7: Sponsor's summary of therapy given after withdrawal from trial treatment

Therapy	Number of patients (%)	
	Anastrozole 1 mg [n = 235]	Tamoxifen 20 mg [n = 241]
Radiotherapy	73 (31.1%)	77 (32.0%)
Chemotherapy	106 (45.1%)	105 (43.6%)
Hormonal therapy	117 (49.8%)	142 (58.9%)
Other	52 (22.1%)	49 (20.3%)

2.4 REVIEWER'S ANALYSIS RESULTS AND CONCLUSION

This reviewer analyzed time to progression, objective response rate and survival based on the sponsor's/medical officer's data. Results are summarized as below. This reviewer also explored the age effect on these endpoints and results are attached in Appendix (Section 5.2.1).

2.4.1 Primary Endpoint: Time to Progression

The medical officer evaluated time to progression for each patient. Results based on the medical officer's data are summarized in this section.

Using the ITT population, a total of 495 (74.1%) patients had disease progression. Of these, 250 patients were randomized to anastrozole and 245 patients to tamoxifen. The estimated median time to progression was 249 days for patients randomized to anastrozole and 246 days for patients randomized to tamoxifen. The results of statistical analysis were very similar to those based on the sponsor's data (see Table 8). The Kaplan-Meier probability plot of time to progression is shown in Figure 5.

Using the PP population (secondary approach), 581 patients were included in this population. Of these, 290 (49.9%) patients were randomized to anastrozole and 291 (50.1%) patients to tamoxifen. A total of 434 (74.7%) patients had disease progression. Of these, 218 patients were randomized to anastrozole and 216 patients to tamoxifen. The estimated median time to progression was 249 days for patients randomized to anastrozole and 246 days for patients randomized to tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 8).

Table 8: Reviewer's results of TTP based on MO's and Sponsor's data

Population	Analysis (Tamoxifen: anastrozole)	Data source	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	MO	0.98	0.84	(0.82, 1.17)	0.82
		Sponsor	0.99	0.86	(0.83, 1.19)	0.94
	Unadjusted ^c	MO	1.00	0.86	(0.83, 1.19)	0.95
		Sponsor	1.01	0.87	(0.85, 1.20)	0.92
PP	Adjusted	MO	0.96	0.82	(0.80, 1.16)	0.67
		Sponsor	0.97	0.83	(0.80, 1.17)	0.74
	Unadjusted	MO	0.97	0.83	(0.81, 1.17)	0.77
		Sponsor	0.98	0.84	(0.81, 1.18)	0.84

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

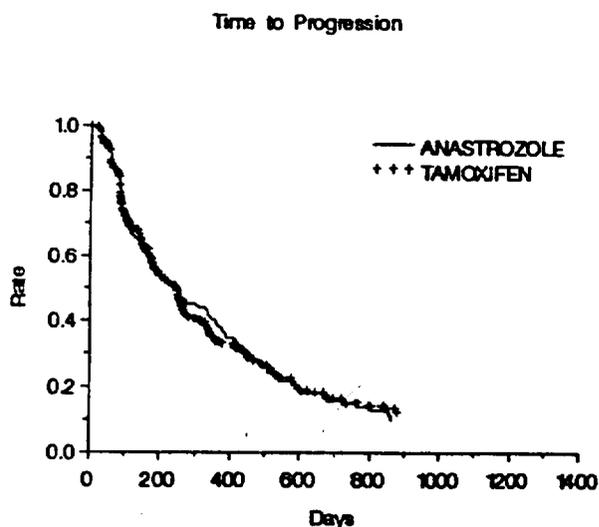
^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H_0 : hazard ratio = 1 against H_1 : hazard ratio \neq 1.

REVIEWER'S CONCLUSION:

- Results based on the medical officer's re-adjudication of this endpoint were consistent with those based on the sponsor's data.

Figure 5: Reviewer's Kaplan-Meier probability of TTP using ITT population based on MO's data



2.4.2 Primary Endpoint: Objective response Rate

This reviewer used a more robust approach¹, without assuming a logistic regression model, to assessing the non-inferiority in this endpoint. The corresponding lower 1-sided 95% confidence limit of the estimated difference in response rates is

where \hat{p}_1 is the estimated response rate in the anastrozole group and \hat{p}_2 the tamoxifen group; n_1 is the number of patients in the anastrozole group and n_2 the tamoxifen group.

The last term in the confidence limit expression, $\frac{1}{\sqrt{1 + \frac{1}{n_1} + \frac{1}{n_2}}}$ is a correction factor to better

approximate the binomial distribution of responses to the normal distribution. This reviewer's results for both ITT and PP populations are summarized in Table 9. As seen in this table, the lower one-sided 95% confidence limits were greater than -10%, supporting the sponsor's claim of non-inferiority in this endpoint.

This reviewer also obtained a two-sided confidence interval of the difference in response rates, given by

and the corresponding p-value. The results (also summarized in Table 9) showed that there was no evidence of treatment difference in objective response rate. The lower limit of the two-sided 95% confidence interval was also greater than -10%.

Table 9: Reviewer's statistical analysis of objective response rate

Population	Estimated difference in Response rate ^a (anastrozole - tamoxifen)	One-sided lower 95% CL	Two-sided 95% CI	P-value ^b
Anastrozole : tamoxifen				
ITT population	0.32% (32.94% - 32.62%)	-5.96%	(-7.10%, 7.74%)	0.996
PP population	-1.26% (33.45% - 34.71%)	-8.07%	(-9.31%, 6.79%)	0.816

^a Difference in response ratios of greater [less] than 0 indicate that anastrozole was associated with a higher [lower] response rate than was tamoxifen.

^b Based on a two-sided test for H_0 : difference in response rate (anastrozole - tamoxifen) = against difference: A smaller p-value indicates a stronger evidence for unequal response rates.

¹ Joseph L. Fleiss, Statistical Methods for Rates and proportions, 2nd edition, John Wiley & Sons, New York. , 1981.

CONCLUSION:

This reviewer's results were consistent with the sponsor's.

2.4.3 Secondary Endpoint: Time to Death (Survival)

Using the intent-to-treat population, at the second time of data cut-off, the Kaplan-Meier estimate for the median time was 1145 days for the anastrozole group and 1246 days for the tamoxifen group. The adjusted analysis (the protocol specified primary analysis) resulted in an estimated hazard ratio (tamoxifen: anastrozole) of 0.87 with a p-value of 0.29 at the second time of data cut-off, as compared to a hazard ratio of 0.76 with a p-value of 0.09 at the first time of data cut-off. This suggested that tamoxifen was associated with a reduction (compared with anastrozole) in the "instantaneous" risk of death by 24% before survival data were updated, but by only 13% after survival data were updated. The results from the unadjusted analysis were similar to those from the adjusted analysis. Table 10 summarizes the reviewer's analysis results.

Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 10).

Table 10: Reviewer's statistical analysis of survival

Population	Data cut-off date	Comparison	Hazard ratio ^a	P-value ^b	95% two-sided CI
		Tamoxifen: anastrozole			
ITT	March 10, 1999	Adjusted analysis ^c	0.76	0.09	(0.56, 1.04)
		Unadjusted analysis ^d	0.79	0.12	(0.58, 1.07)
	February 23, 2000	Adjusted analysis	0.87	0.29	(0.68, 1.11)
		Unadjusted analysis	0.90	0.41	(0.70, 1.16)
PP	March 10, 1999	Adjusted analysis	0.72	0.06	(0.51, 1.01)
		Unadjusted analysis	0.73	0.07	(0.52, 1.03)
	February 23, 2000	Adjusted analysis	0.83	0.17	(0.63, 1.08)
		Unadjusted analysis	0.85	0.23	(0.65, 1.11)

^a Hazard ratios of less than 1.00 indicate that anastrozole was associated with a shorter survival time than was tamoxifen.

^b Based on a two-sided test for equal against unequal hazard rates.

^c The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^d The unadjusted analysis was performed using a Cox regression model including treatment factor only.

CONCLUSION:

- The estimated hazard ratios after data were updated were slightly increasing as compared to those before data were updated. However, the study was not designed to show non-inferiority or superiority with respect to survival; therefore, it may not have enough power to detect treatment difference in survival.

2.5 REVIEWER'S SUMMARY CONCLUSION

This reviewer confirmed the sponsor's results on both primary endpoints: time to progression and objective response rate. The study was not designed to show non-inferiority or superiority with respect to survival; therefore, it may not have enough power to detect treatment difference in survival.

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3 TRIAL 1033IL/030

3.1 TITLE

A Randomized, double blind trial to compare the efficacy and safety of anastrozole (ARIMDEX™ 1 mg daily) with tamoxifen citrate (20 mg daily) as first-line therapy for advanced breast cancer in postmenopausal women.

3.2 DESCRIPTION OF TRIAL 1033IL/0030

3.2.1 Objective

The objective of this study was to compare the efficacy and safety of anastrozole (1mg od) with tamoxifen (20mg od) as first line therapy for advanced breast cancer in postmenopausal women.

3.2.2 Design

Trial 1033IL/0030 is a randomized, double blind, multi-center, double dummy, Phase III study comparing two arms:

- (a) anastrozole (1mg orally od) plus tamoxifen placebo
- (b) tamoxifen (20mg orally od) plus anastrozole placebo

for the first line therapy of advanced breast cancer in postmenopausal women. A separate randomization scheme, incorporating 2 levels of stratification (soft tissue and/or lung disease only vs. all other disease combinations) will be prepared for each center by the sponsor. Patients were allocated to treatment in balanced blocks.

Therapy was initiated on the date of randomization (Visit 1). Patients were treated until evidence of objective progression of disease. Patients were reviewed for safety and efficacy at 4 week intervals up to 12 weeks and every 12 weeks thereafter. Assessments continued until objective progression of disease is assigned irrespective of whether trial therapy had been withdrawn prior to progression. After withdrawal, patients were reviewed at 6 month intervals for survival until death. Additionally, patients who withdrew due to an adverse event will have tumor assessments every 3 months until disease progression.

The first patient was recruited on February 26, 1995 and the last patient on July 9, 1998. Data were cut off on March 10, 1999.

3.2.3 Patient Population (Protocol)

See Section 2.2.3 for Trial 0027.

3.2.4 Efficacy Endpoints

The primary efficacy endpoints are the same as those in Trial 0027 (time to progression and objective response rate). The secondary efficacy endpoints include those in Trial 0027 (time to treatment failure, time to death, duration of response, duration of clinical benefit, health economics) and three subjective endpoints: analgesic use, WHO performance scores and bone pain. For definitions of endpoints that also appeared in Trial 0027, please refer to Section 2.2.4.

3.2.5 Interim Analysis

No interim analysis was planned.

3.2.6 Statistical Methods (Protocol)

For endpoints that also appeared in Trial 0027, please refer to Section 2.2.6. For the three subjective endpoints (analgesic use, WHO performance scores and bone pain), logistic regression models with the same baseline covariates as described for objective response rate will be used. Treatments for these subjective endpoints will be compared using the odds ratio, the corresponding two-sided 95% confidence limits and the associated p-value.

3.3 SPONSOR'S RESULTS AND REVIEWER'S COMMENTS

Three hundred fifty three patients were randomized and included in the primary (ITT) analyses for all efficacy endpoints. Among those a total of 70 (19.8%) patients were considered to be significant protocol violators or deviators, or both. Of these, 38 patients were randomized to anastrozole and 32 patients to tamoxifen. After excluding the 70 patients, a total of 283 (80.2%) patients were included in the secondary (per-protocol) analysis.

The sponsor's results of patients' baseline characteristics and of efficacy endpoints are summarized in the following sections. This reviewer's comments will be included as needed.

3.3.1 Baseline Characteristics

A total of 353 female patients in North America were randomized to trial treatment. Of those, 171 patients were randomized to anastrozole and 182 to tamoxifen. Table 11 summarizes the sponsor's results of demographic details for age, height, weight, BMI, and ethnic origin for all patients at entry. The results showed that demographic characteristics in the two treatment groups were similar to each other.

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Table 11: Sponsor's demographic characteristics

Demographic characteristic		Treatment group	
		anastrozole 1 mg [n=171]	Tamoxifen 20 mg [n=182]
Age (years)	Mean	67	66
	SD	11.8	11.2
	≤ 65 [n (%)]	74 (43.3%)	76 (41.8%)
	> 65 [n (%)]	97 (56.7%)	106 (58.2%)
Height (cm)	n (%)	165 (96.5%)	173 (95.1%)
	Mean	160	160
	SD	7.8	7.2
Weight (kg)	n (%)	168 (98.2%)	178 (97.8%)
	Mean	73	71
	SD	15.2	17.6
Body mass index (kg/m ²)	n (%)	163 (95.3%)	172 (94.5%)
	Mean	28	28
	SD	6.1	6.6
Ethnic origin [n (%)]	Caucasian	152 (88.9%)	160 (87.9%)
	Afro-Caribbean	8	11
	Asian/Oriental	1	1
	Hispanic	5	8
	Other ^a	5	2

^a Other includes patients of mixed origin.

3.3.2 Primary Efficacy Endpoints

3.3.2.1 Time to Progression (TTP)

Using the ITT population (primary approach), a total of 252 (71.4%) patients had disease progression. Of these, 114 patients were randomized to anastrozole and 138 patients to tamoxifen. The estimated median time to progression was 338 days for patients randomized to anastrozole and 170 days for patients randomized to tamoxifen.

Table 12 is the sponsor's results of time to progression analysis. The sponsor's adjusted analysis showed that the tamoxifen: anastrozole comparison had a hazard ratio of 1.44, indicating that the "instantaneous" risk in disease progression for patients who received tamoxifen was increased by 44% compared to that for patients who received anastrozole. The lower 1-sided 95% confidence limit for the hazard ratio was 1.16, which was greater than the statistical criterion of 0.80 required to declare non-inferiority. Similar results were obtained from the unadjusted analysis, which gave a hazard ratio of 1.42 and a lower 95% confidence limit of 1.15. The sponsor's Kaplan-Meier probability plot of time to progression is shown in Figure 6.

Using the PP population (secondary approach), 283 patients were included in this population. Of these, 133 (47.0%) patients were randomized anastrozole and 150 (53.0%) patients to tamoxifen. A total of 198 (70.0%) patients had disease progression. Of these, 85 patients were randomized anastrozole and 113 patients to tamoxifen. The estimated median time to progression was 407 days for patients who received anastrozole and 170 days for patients who received tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 12).

Table 12: Sponsor's statistical analysis of TTP

Populations	Comparison	Hazard ratio ^a	Lower 95% CL
	Tamoxifen: anastrozole		
ITT	Adjusted analysis ^b	1.44	1.16
	Unadjusted analysis ^c	1.42	1.15
PP	Adjusted analysis	1.53	1.21
	Unadjusted analysis	1.51	1.19

^a Hazard ratios of greater than 1.00 indicate that anastrozole was associated with a longer time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

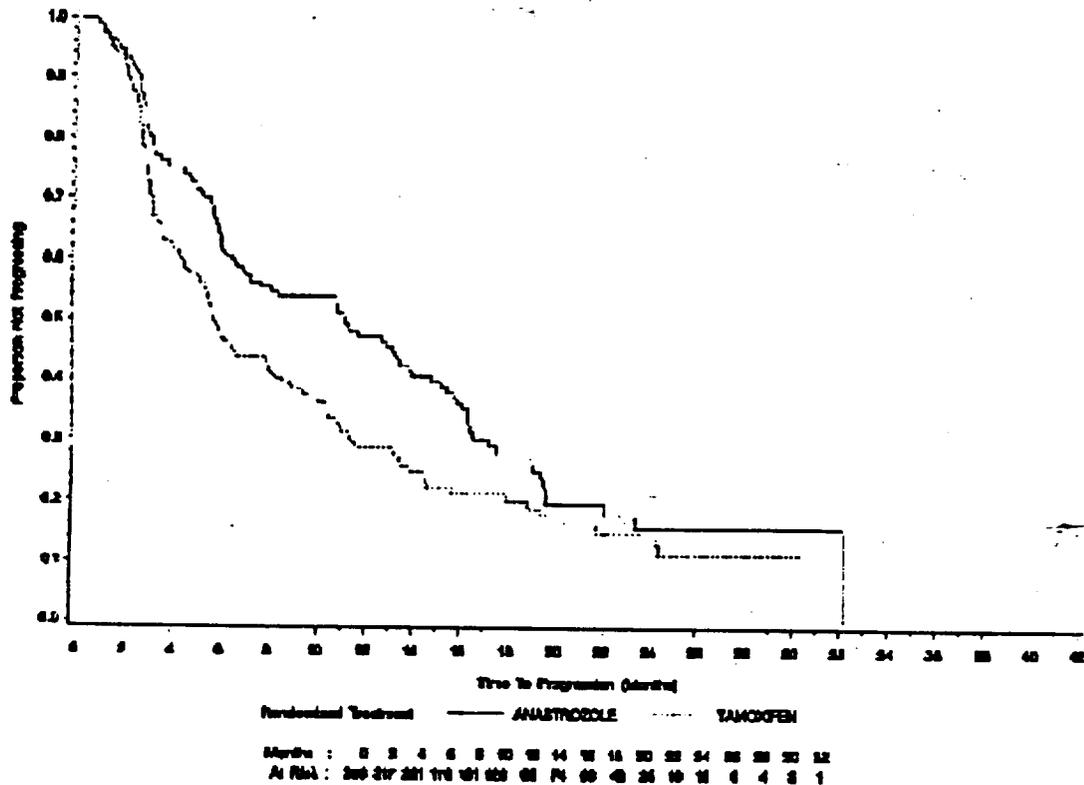
REVIEWER'S COMMENTS:

- This reviewer confirmed the sponsor's results. Both adjusted and unadjusted analyses led to consistent results.
- The medical officer evaluated this endpoint for each patient. The results were very similar to those based on the sponsor's data.
- This reviewer also obtained the two-sided 95% confidence intervals and p-values for the hazard ratio using MO's and Sponsor's data, respectively. Both data suggested that anastrozole was significantly better (p-value < 0.01) than tamoxifen in time to progression.

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Figure 6: Sponsor's Kaplan-Meier probability of TTP using ITT population



3.3.2.2 Objective response (CR or PR) Rate

Using the intent-to-treat population, the best objective-response rate of CR or PR was slightly higher for patients randomized to anastrozole (21.1% [36/171]) than for patients randomized to tamoxifen (17.0% [31/182]). Table 13 is the sponsor's summary of objective response using the ITT population.

Table 14 summarizes the sponsor's results of statistical analysis of objective-response rate. Results of the adjusted analysis showed that the estimated difference in response rates (1.38%) favored anastrozole. The lower 1-sided 95% confidence limit for the difference rate (anastrozole – tamoxifen) was -1.90%, which was greater than the statistical criterion of -10% to declare non-inferiority. Consistent results were observed from the unadjusted analysis, with an estimated difference in response rates of 4.02% and a lower 95% confidence limit of -2.47% which again fell within the statistical criterion for determining non-inferiority. Therefore, the sponsor concluded that anastrozole was non-inferior to tamoxifen in terms of objective-response rate.

The sponsor's results from the per-protocol analysis were consistent with those from the ITT analysis. The proportion of patients who had a best objective-response rate of CR or PR was

similar for patients randomized to receive anastrozole (21.8%), compared with the rate for patients randomized to receive tamoxifen (18.0%). The estimated differences in response rates were 4.64% and 3.80%, from the adjusted and unadjusted analyses, respectively. The lower 1-sided 95% confidence limit for the difference in response rates, was greater than the statistical criterion of -10% from both the adjusted (-3.03%) and unadjusted (-3.43%) analyses (see Table 14).

Table 13: Sponsor's objective response using ITT population

Objective response	Number (%) of patients	
	Anastrozole 1 mg [n = 171]	Tamoxifen 20 mg [n = 182]
Responders	36 (21.1%)	31 (17.0%)
Complete response	5 (2.9%)	5 (2.7%)
Partial response	31 (18.1%)	26 (14.3%)
Non-responders	135 (78.9%)	151 (83.0%)
Stable disease ≥ 24 weeks	65 (38.0%)	52 (28.6%)
Stable disease < 24 weeks	7 (4.1%)	4 (2.2%)
Progression	63 (36.8%)	95 (52.2%)

Table 14: Sponsor's statistical analysis of objective response rate

Population	Logistic regression	Odds ratio ^a	Lower 95% CL	Estimated Difference in Response rate ^b	Lower 95% CL
	Anastrozole : tamoxifen				
ITT	Adjusted analysis ^c	1.38	0.87	5.01%	-1.90%
	Unadjusted analysis ^d	1.30	0.83	4.02%	-2.47%
PP	Adjusted analysis	1.33	0.80	4.64%	-3.03%
	Unadjusted analysis	1.27	0.78	3.80%	-3.43%

^a Odds ratios of greater than 1.00 indicate that anastrozole was associated with a higher response rate than was tamoxifen.

^b Difference in response ratios of greater than 0 indicate that anastrozole was associated with a higher response rate than was tamoxifen.

^c The adjusted analysis was performed using a logistic regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^d The unadjusted analysis was performed using a logistic regression model including treatment factor only.

REVIEWER'S COMMENTS:

- The medical officer evaluated this endpoint for each patient. However, the outcomes (whether responding or not) were identical to the sponsor's classification.
- See Reviewer's Comments in Section 2.3.2.2.

3.3.3 Secondary Efficacy Endpoints

3.3.3.1 Time to Death (Survival)

The survival data in the original NDA submission was cut off on March 10, 1999. Since the original survival data were premature (72% of the 353 patients were censored), the agency requested the sponsor for an updated survival data on July 24, 2000. The updated survival data were received on August 8, 2000; the data were cut off on February 23, 2000.

Using the intent-to-treat population, the death rate, as indicated in Table 15, was slightly higher in patients who were randomized to receive anastrozole (26.8%), compared with patients who were randomized to receive tamoxifen (22.6%) at the first time of data cut-off (March 10, 1999). However, the death rate was lower for the anastrozole group (36.8% vs. 41.2%) at the second time of data cut-off (February 23, 2000). The Kaplan-Meier survival curves for both original and updated data are depicted in Figure 7 and Figure 8, respectively.

The protocol (p. 210 in the sponsor's vol. 6.19) specified that "if the median time to death cannot be estimated at the time of submission only Kaplan-Meier curves will be presented for each treatment group." As a result, the sponsor did not perform a statistical analysis of survival at both times of data cut-off.

Results from the per-protocol analysis were similar to those from the ITT analysis.

Table 15: Sponsor's results of number of deaths using ITT population

Data cut-off date	ITT population	
	Anastrozole (N = 171)	Tamoxifen (N = 182)
March 10, 1999	47 (26.8%)	53 (22.6%)
February 23, 2000	63 (36.8%)	75 (41.2%)

REVIEWER'S COMMENTS:

- This reviewer performed a statistical analysis using the original and updated survival data, respectively. The results are summarized in Section 3.4.3.

Figure 7: Kaplan-Meier probability of survival time using ITT population – data cut-off as of March 10, 1999

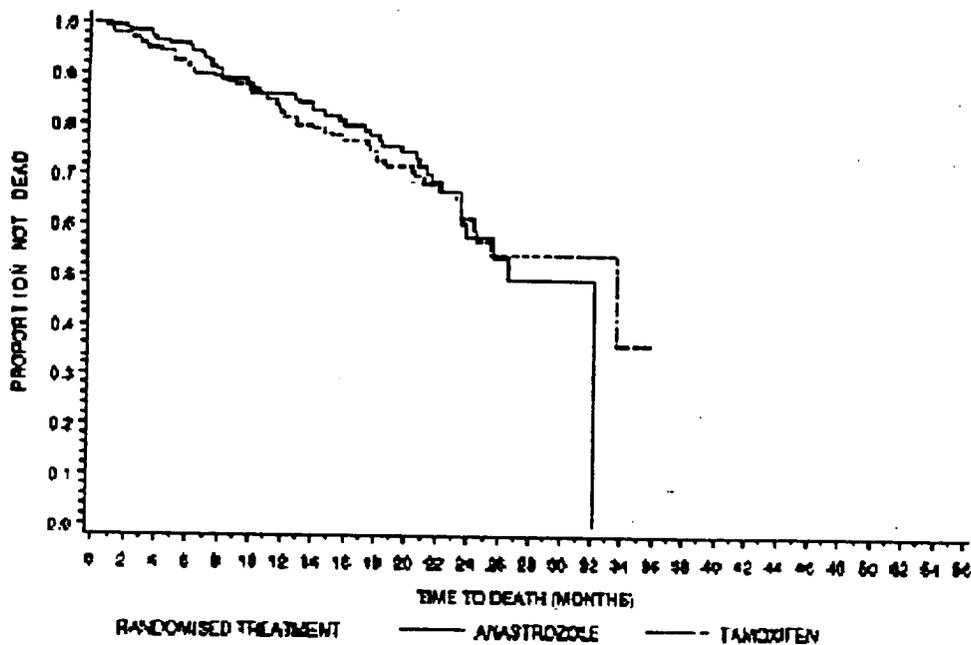
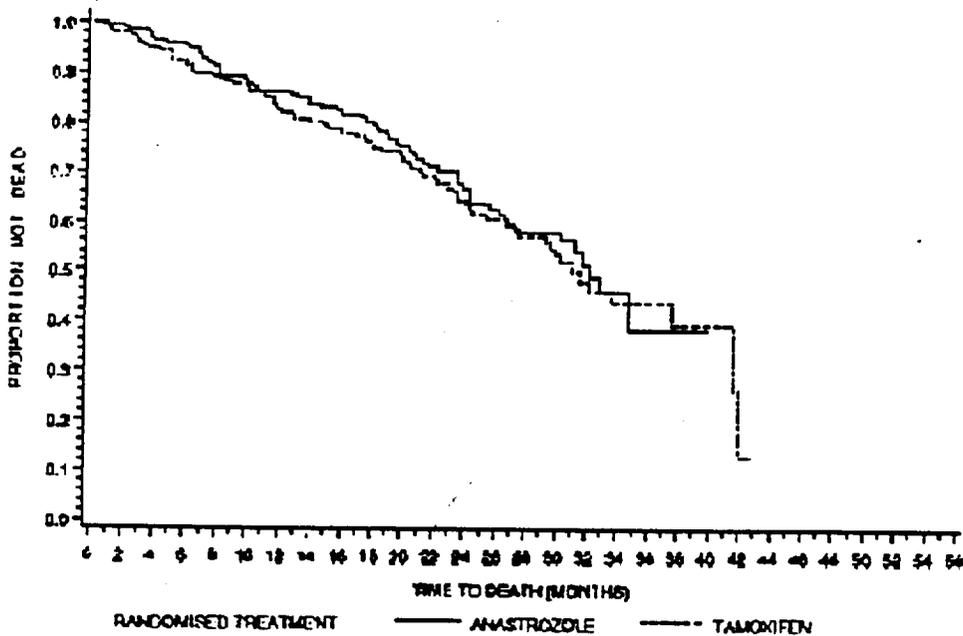


Figure 8: Kaplan-Meier probability of survival time using ITT population – data cut-off as of February 23, 2000



3.3.3.2 Time to Treatment Failure

Of the 353 patients who were randomized to trial treatment, 247 (70.0%) patients had treatment failure resulting from disease progression. 34 (9.6%) patients were withdrawn from the trial for reasons other than disease progression and 6 (1.7%) patients died before progression. This resulted in a total of 287 (81.3%) patients who had treatment failure. A smaller proportion of patients who were randomized to anastrozole (78.9%) had treatment failure, compared with the proportion of patients who were randomized to tamoxifen (83.5%). Patients who were randomized to anastrozole also had a longer estimated median time to treatment failure (231 days), compared with the time for patients who were randomized to tamoxifen (163 days).

The hazard ratio from the adjusted analysis was 1.35 in favor of anastrozole and the lower 1-sided 95% confidence limit for the hazard ratio (tamoxifen: anastrozole) was 1.11, which was greater than the minimum value (0.8) required to demonstrate non-inferiority. Consistent results were observed from the unadjusted analysis, with a hazard ratio of 1.33 and a lower 1-sided 95% confidence limit of 1.10. Table 16 is the summary of the sponsor's statistical analysis of time to treatment failure using ITT population. The sponsor's Kaplan-Meier plot for time to treatment failure is presented in Figure 9.

Table 16: Sponsor's statistical analysis of time to treatment failure using ITT population

Comparison	Hazard ratio ^a	Lower 95% CL
Tamoxifen: anastrozole		
Adjusted analysis ^b	1.35	1.11
Unadjusted analysis ^c	1.33	1.10

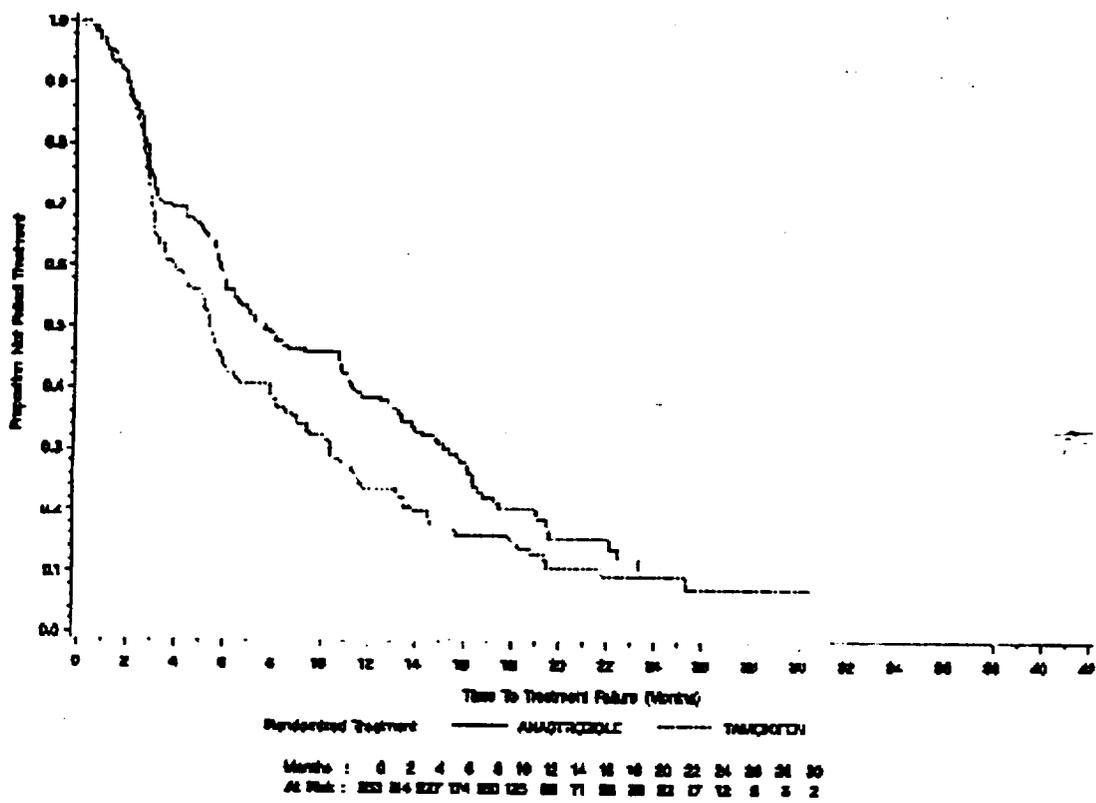
^a Hazard ratios of greater than 1.00 indicate that anastrozole was associated with a longer time to death than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

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Figure 9: Sponsor's Kaplan-Meier probability of time to treatment failure using ITT population



3.3.3.3 Duration of Response

Duration of response was assessed in responders only (patients who had an objective response of CR or PR) in 2 ways:

- from the date of randomization to the date of first determined progression or death from any cause, and
- from the date of first documentation of response to the date of first determined progression or death from any cause.

Overall, 67/353 (19.0%) patients were considered to be responders. Of these, 36 responders were randomized to anastrozole and 31 responders were randomized to tamoxifen. The estimated Kaplan-Meier median duration of response from the date of randomization was 490 days (duration range from 63 to 917 days) for responders randomized to anastrozole. The estimated Kaplan-Meier median duration of response from the date of randomization was 546 days (duration range from 84 to 924 days) for responders randomized to tamoxifen. The estimated Kaplan-Meier median duration of response from the date of first documentation of response was 376 days (duration range from 34 to 833 days) for responders randomized to anastrozole. The estimated Kaplan-Meier median duration of response from the date of first documentation was 332 days (duration range from 54 to 784 days) for responders randomized to tamoxifen.

REVIEWER'S COMMENTS:

- Same comments as in Section 2.3.3.3.

3.3.3.4 Duration of Clinical Benefit

Duration of clinical benefit was assessed in patients who experienced clinical benefit, defined as patients who had CR, PR, or SD \geq 24 weeks.

A total of 184/353 (52.1%) patients demonstrated clinical benefit. Of these, 101 patients were randomized to anastrozole and 83 patients were randomized to tamoxifen. The estimated median duration of clinical benefit was 503 days (duration range from 63 to 917 days) for those who experienced clinical benefit and were randomized to anastrozole, and 442 days (duration range from 77 to 924 days) for those who experience clinical benefit and were randomized to tamoxifen.

REVIEWER'S COMMENTS:

- Same comments as in Section 2.3.3.4.

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3.3.3.5 Health Economics

Table 17 summarizes the sponsor's results of the number of patients who were given therapies or who required hospitalization or outpatient visit following the withdrawal of trial treatment. This table presents treatment given to the 264 patients who had withdrawn from the trial by the time of data cut-off. A greater proportion of patients who were randomized to anastrozole received radiotherapy after withdrawal, compared with patients who were randomized to tamoxifen (27.9% and 19.7%, respectively). In contrast, a smaller proportion of patients who were randomized to anastrozole received chemotherapy or hormonal therapy after withdrawal (29.5% and 45.1%, respectively), compared with patients who were randomized to tamoxifen (37.3% and 56.3%, respectively). The proportions of patients who received other therapies were similar between the 2 treatment groups.

Table 17: Sponsor's summary of therapy given after withdrawal from trial treatment

Therapy	Number of patients (%)	
	Anastrozole 1 mg [n = 122]	Tamoxifen 20 mg [n = 142]
Radiotherapy	34 (27.9%)	28 (19.7%)
Chemotherapy	36 (29.5%)	53 (37.3%)
Hormonal therapy	55 (45.1%)	80 (56.3%)
Other	31 (25.4%)	29 (20.4%)

3.3.3.6 Analgesic Use

Analgesic use during this trial was evaluated at Weeks 12 and 24. Approximately 49% of the patients who were randomized to anastrozole and 47% of the patients who were randomized to tamoxifen did not require the use of analgesics at Week 12. Similarly, approximately 52% of the patients who were randomized to anastrozole and 50% of the patients who were randomized to tamoxifen did not require the use of analgesics at Week 24. The percentages of patients who required nonnarcotic agents, oral narcotic agents, or injectable narcotics were similar between the 2 treatment groups at both time points. Table 18 is the sponsor's statistical analysis of analgesic use at Weeks 12 and 24. Formal treatment comparisons were performed using a logistic-regression model with baseline scores at Weeks 12 and 24. No statistically significant difference was found between the 2 treatment groups for analgesic use at Weeks 12 and 24.

Table 18: Sponsor's statistical analysis of analgesic use

Time point	Anastrozole 1 mg versus tamoxifen 20 mg ^b		
	Odds ratio ^a	95% CI	p-value ^c
Week 12	1.13	0.67 to 1.90	0.66
Week 24	1.11	0.62 to 1.99	0.73

^a Odds ratios greater than 1.00 indicate that anastrozole was associated with less aggressive analgesic use than was tamoxifen.

^b The analysis was performed using a logistic-regression model including factors for the baseline score.

^c The critical p-value for statistical significance was 0.05.

3.3.3.7 WHO (World Health Organization) Performance Status

World Health Organization performance status was assessed at Weeks 12 and 24. Approximately 91% of the patients who were randomized to anastrozole and 82% of the patients who were randomized to tamoxifen were either fully active and able to carry on all pre-disease performance without restriction (WHO performance status = 0) or restricted in physically strenuous activity but ambulatory and able to perform work of a light or sedentary nature (WHO performance status = 1) at Week 12. At Week 24, approximately 93% of the patients who were randomized to anastrozole and 87% of the patients who were randomized to tamoxifen had WHO performance scores of 0 or 1. The percentages of patients who had WHO performance scores of 3 or 4 were generally similar between the 2 treatment groups at both time points. Table 19 is the sponsor's summary of the WHO performance status at Weeks 12 and 24. Formal treatment comparisons were performed using a logistic-regression model with baseline scores at Weeks 12 and 24. No statistically significant difference was found between the 2 treatment groups for WHO performance status at Weeks 12 and 24.

Table 19: Sponsor's statistical analysis of WHO performance status

Time point	Anastrozole 1 mg versus tamoxifen 20 mg ^b		
	Odds ratio ^a	95% CI	p-value ^c
Week 12	1.21	0.72 to 2.03	0.48
Week 24	1.20	0.68 to 2.12	0.53

^a Odds ratios greater than 1.00 indicate that anastrozole was associated with a better performance status than was tamoxifen.

^b The analysis was performed using a logistic-regression model including factors for the baseline score.

^c The critical p-value for statistical significance was 0.05.

3.3.3.8 Bone Pain

Bone pain during this trial was assessed at Weeks 12 and 24. Approximately 82% of the patients who were randomized to anastrozole and 80% of the patients who were randomized to tamoxifen had no bone pain or mild bone pain at Week 12. Similarly, approximately 88% of the patients who were randomized to anastrozole and 85% of the patients who were randomized to tamoxifen had no bone pain or mild bone pain at Week 24. It should be noted that 65.5% of patients who were randomized to anastrozole had bone metastases, compared with only 53.8% of the patients who were randomized to tamoxifen. The percentages of patients who had moderate or severe pain were similar between the 2 treatment groups at both time points.

Table 20 is the sponsor's summary of bone pain at Weeks 12 and 24. Formal treatment comparisons were performed using a logistic regression model with a baseline score at Weeks 12 and 24. No statistically significant difference was found between the 2 treatment groups for bone pain at Weeks 12 and 24.

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Table 20: Sponsor's statistical analysis of bone pain scores

Time point	Anastrozole 1 mg versus tamoxifen 20 mg ^b		
	Odds ratio ^a	95% CI	p-value ^c
Week 12	0.96	0.57 to 1.61	0.86
Week 24	1.12	0.61 to 2.05	0.72

^a Odds ratios greater than 1.00 indicate that anastrozole was associated with less bone pain than was tamoxifen.

^b The analysis was performed using a logistic-regression model including factors for the baseline score.

^c The critical p-value for statistical significance was 0.05.

3.4 REVIEWER'S ANALYSIS RESULTS AND CONCLUSION

This reviewer analyzed time to progression, objective response rate and survival based on the sponsor's/medical officer's data. Results are summarized as below. This reviewer also explored the age effect on these endpoints and results are attached in Appendix (Section 5.2.2).

3.4.1 Primary Endpoint: Time To Progression (TTP)

The medical officer re-adjudicated time to progression for each patient. Results based on the medical officer's data are summarized in this section.

Using the ITT population (primary approach), a total of 276 (78.2%) patients had disease progression. Of these, 128 patients were randomized to anastrozole and 148 patients to tamoxifen. The estimated median time to progression was 255 days for patients randomized to anastrozole and 168 days for patients randomized to tamoxifen. The results of statistical analysis were very similar to those based on the sponsor's data (see Table 21). The Kaplan-Meier probability plot of time to progression is shown in Figure 10.

Using the PP population (secondary approach), 283 patients were included in this population. Of these, 133 (47.0%) patients were randomized anastrozole and 150 (53.0%) patients to tamoxifen. A total of 219 (77.4%) patients had disease progression. Of these, 95 patients were randomized anastrozole and 124 patients to tamoxifen. The estimated median time to progression was 336 days for patients who received anastrozole and 168 days for patients who received tamoxifen. Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 21).

REVIEWER'S CONCLUSION:

- Results based on the medical officer's re-adjudication of this endpoint were consistent with those based on the sponsor's data.
- The p-values for the two-sided test were less than 0.01 and the two-sided confidence intervals lied above 1.0. This indicated that anastrozole was significantly better than tamoxifen in time to progression.

Table 21: Reviewer's results of TTP based on MO's and Sponsor's data

Population	Analysis (Tamoxifen: anastrozole)	Data source	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	MO	1.43	1.17	(1.12, 1.82)	0.004
		Sponsor	1.44	1.16	(1.12, 1.85)	0.005
	Unadjusted ^c	MO	1.39	1.14	(1.09, 1.76)	0.007
		Sponsor	1.42	1.15	(1.11, 1.82)	0.006
PP	Adjusted	MO	1.61	1.28	(1.23, 2.12)	<0.001
		Sponsor	1.54	1.21	(1.15, 2.04)	0.003
	Unadjusted	MO	1.56	1.24	(1.19, 2.04)	0.001
		Sponsor	1.51	1.19	(1.13, 2.00)	0.005

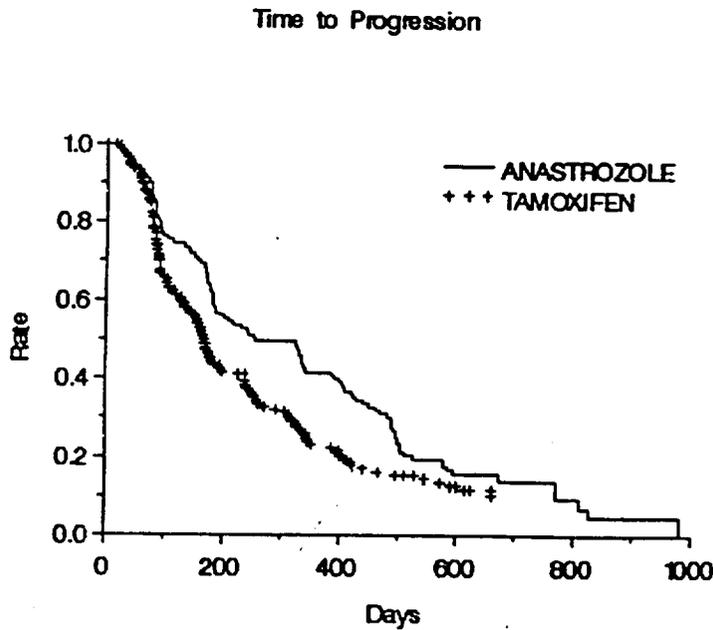
^a Hazard ratios of greater than 1.00 indicate that anastrozole was associated with a longer time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H_0 : hazard ratio = 1 against H_1 : hazard ratio \neq 1.

Figure 10: Reviewer's Kaplan-Meier probability of TTP using ITT population based on MO's data



3.4.2 Primary Endpoint: Objective response Rate

For the same reason as described in Section 2.4.1, this reviewer used a more robust approach to evaluating this dichotomous endpoint. This reviewer's results for both ITT and PP populations are summarized in Table 22. As seen in this table, the lower 1-sided 95% confidence limits were greater than -10%, supporting the sponsor's claim of non-inferiority in this endpoint.

Table 22: Reviewer's statistical analysis of objective response rate

Population	Estimated difference in Response rate ^a (anastrozole - tamoxifen)	One-sided lower 95% CL	Two-sided 95% CI	P-value ^b
Anastrozole : tamoxifen				
ITT population	4.01% (21.05% - 17.03%)	-3.43%	(-4.74%, 12.78%)	0.409
PP population	3.80% (21.80% - 18.00%)	-4.73%	(-6.23%, 13.84%)	0.516

^a Difference in response ratios of greater than 0 indicate that anastrozole was associated with a higher response rate than was tamoxifen.

^b Based on a two-sided test for H_0 : difference in response rate (anastrozole - tamoxifen) = 0 against H_1 : difference \neq 0. A smaller p-value indicates a stronger evidence for unequal response rates.

REVIEWER'S CONCLUSION:

This reviewer results were consistent with the sponsor's.

3.4.3 Secondary Endpoint: Time to Death (Survival)

Using the intent-to-treat population, at the second time of data cut-off, the median time was 980 days for patients who were randomized to anastrozole and 960 days for patients who were randomized to tamoxifen group. The adjusted analysis (the protocol specified primary analysis) resulted in an estimated hazard ratio (tamoxifen: anastrozole) of 1.11 with a p-value of 0.54 at the second time of data cut-off, as compared to a hazard ratio of 1.08 with a p-value of 0.70 at the first time of data cut-off. This suggested that tamoxifen was associated with an increase in the "instantaneous" risk (compared with anastrozole) of death by 8% before survival data were updated, and by 11% after survival data were updated. Results from the unadjusted analysis were similar to those from the adjusted analysis. Table 23 summarizes the reviewer's analysis results.

Results from the per-protocol analysis were consistent with those from the ITT analysis (see Table 23).

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Table 23: Reviewer's statistical analysis of survival

Population	Data cut-off date	Comparison	Hazard ratio ^a	P-value ^b	95% two-sided CI
Tamoxifen: anastrozole					
ITT	March 10, 1999	Adjusted analysis ^c	1.08	0.70	(0.73, 1.61)
		Unadjusted analysis ^d	1.03	0.90	(0.69, 1.53)
	February 23, 2000	Adjusted analysis	1.11	0.54	(0.79, 1.56)
		Unadjusted analysis	1.09	0.63	(0.78, 1.52)
PP	March 10, 1999	Adjusted analysis	1.20	0.45	(0.75, 1.92)
		Unadjusted analysis	1.13	0.62	(0.70, 1.80)
	February 23, 2000	Adjusted analysis	1.28	0.22	(0.86, 1.90)
		Unadjusted analysis	1.25	0.27	(0.84, 1.85)

^a Hazard ratios of less than 1.00 indicate that anastrozole was associated with a shorter survival time than was tamoxifen.

^b Based on a two-sided test for equal against unequal hazard rates.

^c The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^d The unadjusted analysis was performed using a Cox regression model including treatment factor only.

CONCLUSION:

- The estimated hazard ratios before data were updated were greater than 1 and even greater after data were updated, which suggested that patients treated with anastrozole had lower risk of death than those treated with tamoxifen. The study was not designed to show non-inferiority or superiority with respect to survival; therefore, it may not have enough power to detect treatment difference in survival.

3.5 REVIEWER'S SUMMARY CONCLUSION

This reviewer confirmed the sponsor's results on both primary endpoints: time to progression and objective response rate. The study was not designed to show non-inferiority or superiority with respect to survival; therefore, it may not have enough power to detect treatment difference in survival.

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4 REVIEWER'S INTEGRATED SUMMARY AND CONCLUSIONS

4.1 SUMMARY

For both studies 1033IL/0027 and 1033IL/030, the primary efficacy endpoints included objective response rate and time to progression (TTP).

For objective response rate, the sponsor demonstrated, in both studies, that the one-sided lower 95% confidence limit of the difference in response rates was greater than -10% (Table 4 & Table 14). According to the criterion of non-inferiority defined in the protocol, the sponsor concluded that anastrozole was not inferior to tamoxifen in terms of objective response rate.

For TTP, the sponsor demonstrated, in both studies, that the one-sided lower 95% confidence limit of the hazard ratio was greater than 0.8 (Table 2 & Table 12). According to the criterion of non-inferiority defined in the protocol, the sponsor concluded that anastrozole was not inferior to tamoxifen in terms of TTP. Particularly, in study 1033IL/0030, the risk of disease progression was statistically significantly lower for patients randomized to anastrozole, as compared to those randomized to tamoxifen (Table 21).

There was no statistically significant difference in survival detected between the two treatment arms in both studies.

4.2 CONCLUSIONS

The primary objective of this trial was achieved if the non-inferiority of anastrozole to tamoxifen was obtained on both primary endpoints of TTP and objective response rate. According to the criteria of non-inferiority defined in the protocol, the sponsor has demonstrated, in both studies, that anastrozole was not inferior to tamoxifen, in terms of TTP and objective response rate. This reviewer further confirmed the sponsor's results using both one-sided and two-sided 95% lower confidence limits.

The margin for the response rate was defined in the protocol as 10%, i.e., the lower 95% confidence limit of the difference (anastrozole – tamoxifen) should be greater than -10% (0-10%). The margin for TTP was defined in the protocol as 20%, i.e., the lower 95% confidence limit of the hazard ratio (tamoxifen:anastrozole) should be greater than 0.8 (1-0.2). The FDA does not have a general policy on how much of the tamoxifen response rate and the median TTP may be lost with the new hormonal drug and still consider it non-inferior to tamoxifen. This is determined on a case by case basis. Readers are referred to medical team leader's review regarding this issue.

The two studies have provided adequate evidence to demonstrate that the treatment effect of anastrozole may not be worse than tamoxifen in terms of response rate and TTP, despite some concerns regarding the non-inferiority margin selection for TTP. The drug approval should be based on the integrated evidence including the treatment effect, safety, and other relevant clinical judgement.

5 APPENDIX

Section 5.1 describes the sponsor's approaches to obtaining the 95% lower confidence limit of the difference in response rates, using the unadjusted and the adjusted analyses, respectively. Notice that the sponsor's approach based on the adjusted analysis was not acceptable; the approach based on the unadjusted analysis was acceptable, but not preferred.

Section 5.2 summarizes reviewer's analyses of age effect on time to progression, objective response rate, and survival.

5.1 SPONSOR'S APPROACHES TO ANALYSIS OF OBJECTIVE RESPONSE

5.1.1 *Unadjusted logistic regression*

The logistic model is

Table 24: Response rate using unadjusted logistic regression model

Group	Prob. of success (Response rate)	Prob. of failure (Non-response rate)
Tamoxifen		
Anastrozole		

The difference in response rates (anastrozole - tamoxifen) is

The sponsor estimated the 95% lower confidence limit of the difference by

where \hat{p}_i is the crude estimated response rate for group i (i.e. the number of responders divided by the total number of patients in the group).

5.1.2 Adjusted logistic regression

Let X_1, X_2, X_3, X_4 denote the four prognostic factors with values 0 or 1. Let p_i denote the probability of having an objective response (having a success) given any prognostic quadruple set for group i (i is the tamoxifen group, $i=1$ the anastrozole group). The logistic model that includes the terms for the four prognostic factors is

Given a fixed vector of the prognostic quadruple set, the formulas for the odds ratio, the corresponding point estimator and its 95% one-sided lower confidence limit remain the same as in Section 5.1 (unadjusted logistic regression). However, the difference in response rates between the two groups becomes

which depends on the values of the four prognostic factors, so the difference in response rates varies with a different prognostic quadruple set. However, in order to obtain a lower confidence limit, the sponsor estimated p_1 (the response rate given a specific prognostic quadruple set for the tamoxifen group) by a pooled \hat{p}_1 regardless of the prognostic quadruple set. That is, the sponsor estimated the 95% one-sided lower confidence limit of the difference

5.2 SUBGROUP ANALYSES BY AGE GROUP

Since the medical officer's re-adjudication of TTP was very similar to the sponsor's and re-adjudication of objective response was identical to the sponsor's, the age effect on these two endpoints was explored using the sponsor's data. For the age effect on survival, the sponsor's updated data were adopted.

5.2.1 Trial 1033IL/0027

5.2.1.1 Time to Progression (TTP)

Table 25: Reviewer's descriptive summary of TTP by age group

Population	Age	Treatment	N	Failed	Censored (%)	Median time to progression (days)
ITT	≤ 65	Anastrozole	160	122	38 (24%)	182
		Tamoxifen	160	130	30 (19%)	184
	> 65	Anastrozole	180	127	53 (29%)	300
		Tamoxifen	168	111	51 (30%)	301
PP	≤ 65	Anastrozole	137	108	28 (20%)	172
		Tamoxifen	145	117	28 (19%)	182
	> 65	Anastrozole	153	109	44 (29%)	300
		Tamoxifen	146	100	46 (32%)	326

Table 26: Reviewer's analysis of TTP by age group

Population	Analysis (Tamoxifen: anastrozole)	Age	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	≤ 65	1.05	0.85	(0.82, 1.34)	0.70
		> 65	0.92	0.74	(0.71, 1.19)	0.53
	Unadjusted ^c	≤ 65	1.05	0.85	(0.82, 1.34)	0.72
		> 65	0.96	0.78	(0.75, 1.24)	0.77
PP	Adjusted	≤ 65	1.00	0.81	(0.77, 1.30)	0.98
		> 65	0.94	0.74	(0.71, 1.24)	0.65
	Unadjusted	≤ 65	1.00	0.81	(0.77, 1.30)	0.99
		> 65	0.94	0.75	(0.72, 1.23)	0.65

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H_0 : hazard ratio = 1 against H_1 : hazard ratio \neq 1.

Figure 11: Reviewer's Kaplan-Meier probability of TTP using ITT population (age ≤ 65)

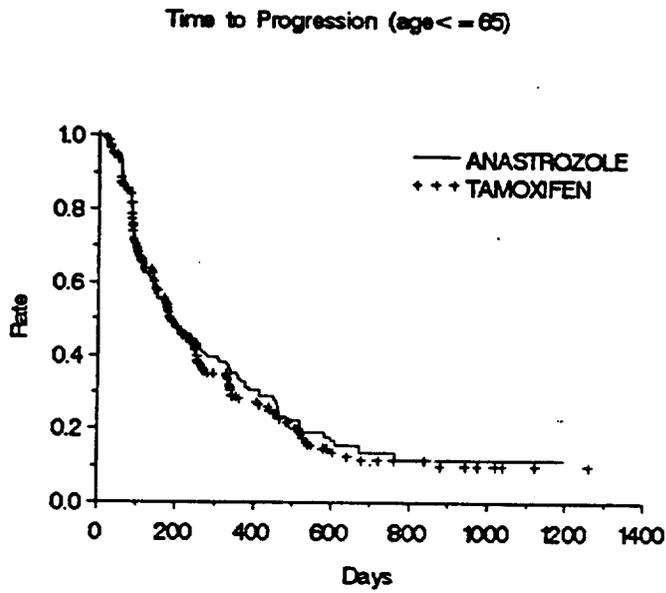


Figure 12: Reviewer's Kaplan-Meier probability of TTP using ITT population (age > 65)

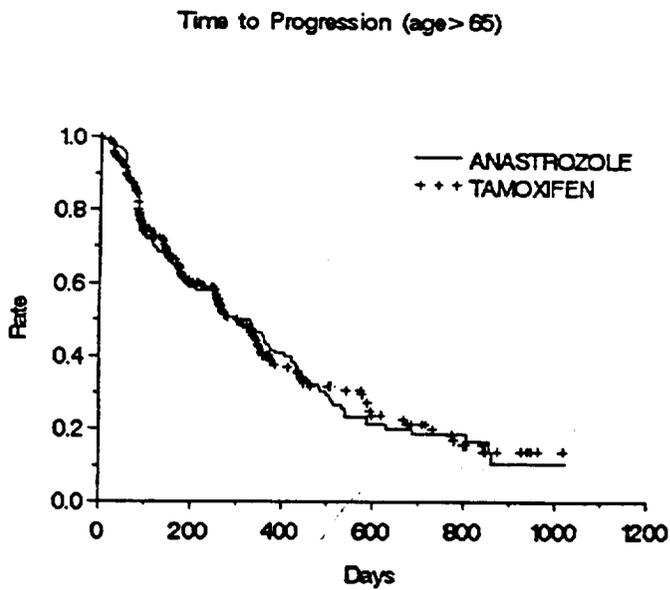


Figure 13: Reviewer's Kaplan-Meier probability of TTP using PP population (age ≤ 65)

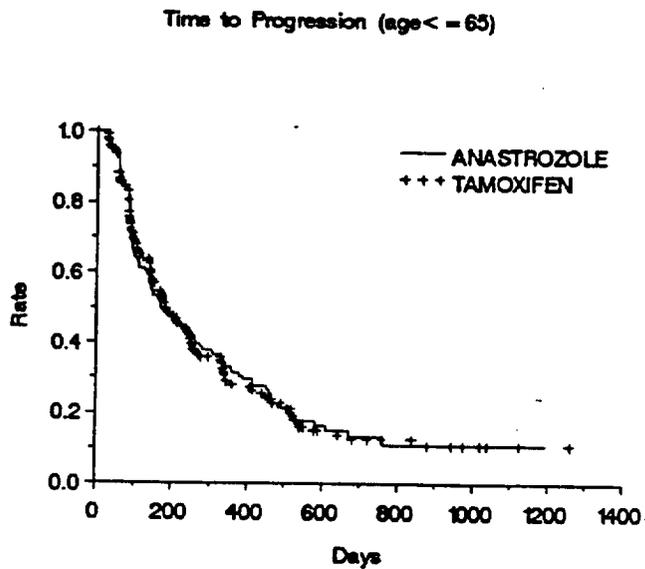
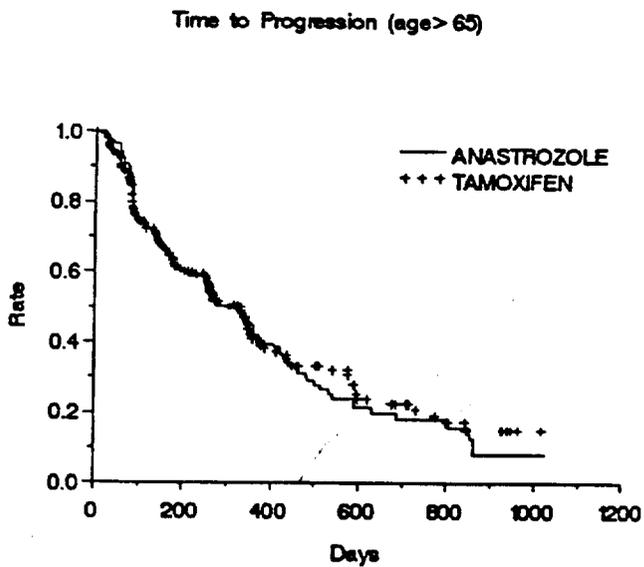


Figure 14: Reviewer's Kaplan-Meier probability of TTP using PP population (age > 65)



5.2.1.2 Objective response Rate

Table 27: Reviewer's descriptive summary of objective response by age group

Population	Age	Treatment	N	Responses (%)	Difference in response rate (anastrozole – tamoxifen)
ITT	≤ 65	Anastrozole	160	46 (29%)	3.10%
		Tamoxifen	160	41 (26%)	
	> 65	Anastrozole	180	66 (37%)	-2.62%
		Tamoxifen	168	66 (39%)	
PP	≤ 65	Anastrozole	137	41 (30%)	2.34%
		Tamoxifen	145	40 (28%)	
	> 65	Anastrozole	153	56 (37%)	-5.18%
		Tamoxifen	146	61 (42%)	

Table 28: Reviewer's analysis of objective response by age group

Population	Age	Difference in response rate (anastrozole – tamoxifen)	One-sided lower 95% CL	Two-sided 95% CI	P-value ^a
ITT	≤ 65	3.10%	-5.68%	(-7.24%, 13.50%)	0.615
	> 65	-2.62%	-11.76%	(-13.40%, 8.16%)	0.695
PP	≤ 65	2.34%	-7.24%	(-8.93%, 13.62%)	0.762
	> 65	-5.18%	-15.13%	(-16.91%, 6.54%)	0.424

^a Based on a two-sided test for H₀: difference in response rate = 0 against H₁: difference ≠ 0.

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5.2.1.3 Time to Death (Survival)

Table 29: Reviewer's descriptive summary of survival by age group

Population	Age	Treatment	N	Failed	Censored (%)	Median time to death (days)
ITT	≤ 65	Anastrozole	160	61	99 (62%)	1103
		Tamoxifen	160	61	99 (62%)	1217
	> 65	Anastrozole	180	67	113 (63%)	NA
		Tamoxifen	168	58	110 (65%)	1246
PP	≤ 65	Anastrozole	137	57	80 (58%)	1079
		Tamoxifen	145	53	92 (63%)	1258
	> 65	Anastrozole	153	53	100 (65%)	NA
		Tamoxifen	146	48	98 (67%)	1246

Table 30: Reviewer's analysis of survival by age group

Population	Analysis (Tamoxifen: anastrozole)	Age	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	≤ 65	0.95	0.70	(0.66, 1.35)	0.76
		> 65	0.81	0.60	(0.57, 1.15)	0.24
	Unadjusted ^c	≤ 65	0.94	0.70	(0.66, 1.34)	0.73
		> 65	0.86	0.64	(0.61, 1.22)	0.40
PP	Adjusted	≤ 65	0.80	0.58	(0.55, 1.16)	0.24
		> 65	0.86	0.62	(0.58, 1.27)	0.44
	Unadjusted	≤ 65	0.80	0.59	(0.55, 1.17)	0.25
		> 65	0.89	0.64	(0.60, 1.32)	0.56

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] survival time than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H_0 : hazard ratio = 1 against H_1 : hazard ratio \neq 1.

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Figure 15: Reviewer's Kaplan-Meier probability of survival using ITT population (age ≤ 65)

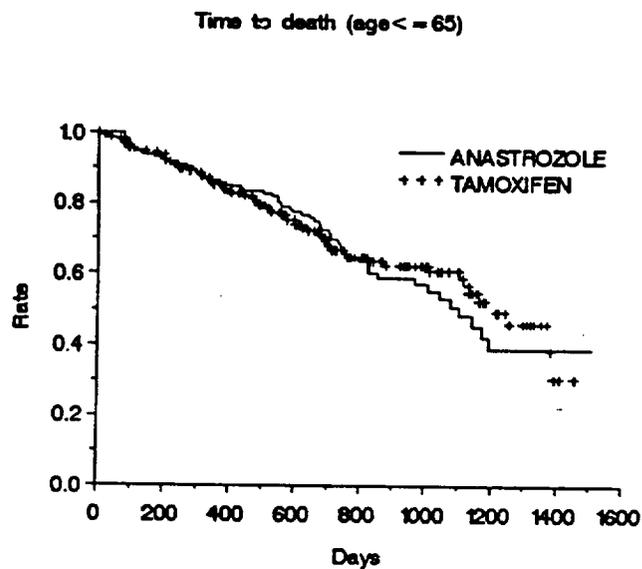


Figure 16: Reviewer's Kaplan-Meier probability of survival using ITT population (age > 65)

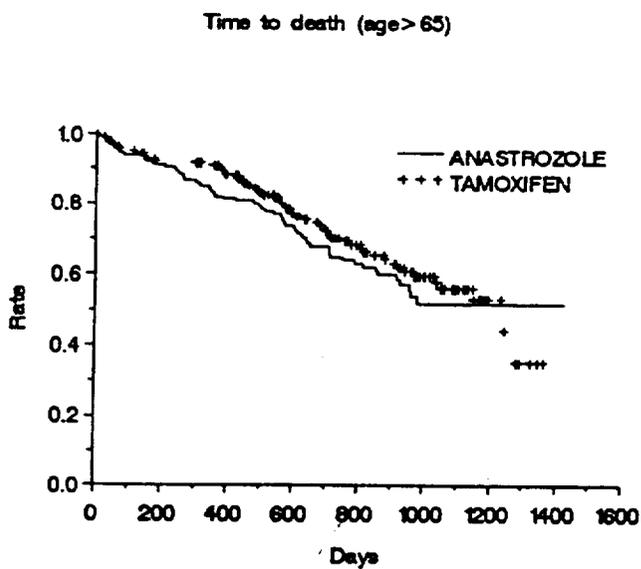


Figure 17: Reviewer's Kaplan-Meier probability of survival time using PP population (age ≤ 65)

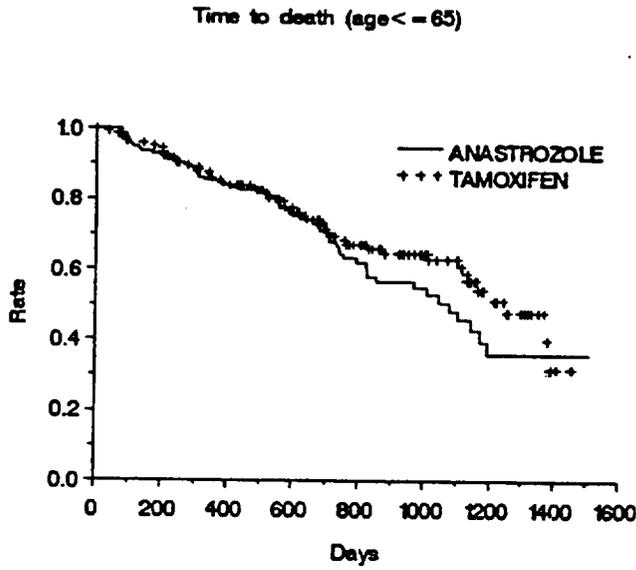
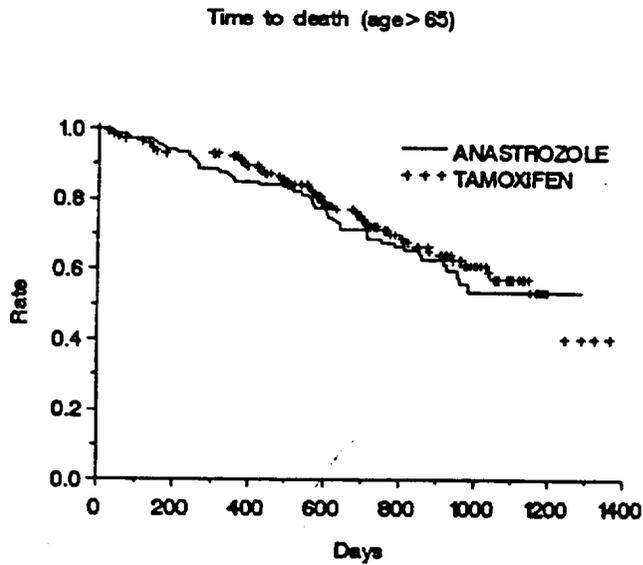


Figure 18: Reviewer's Kaplan-Meier probability of survival time using PP population (age > 65)



5.2.2 Trial 10331I/030

5.2.2.1 Time to Progression (TTP)

Table 31: Reviewer's descriptive summary of TTP by age group

Population	Age	Treatment	N	Failed	Censored	Median time to progression (days)
ITT	≤ 65	Anastrozole	74	55	19 (26%)	201
		Tamoxifen	76	58	18 (24%)	166
	> 65	Anastrozole	97	59	38 (39%)	403
		Tamoxifen	106	80	26 (25%)	196
PP	≤ 65	Anastrozole	57	42	15 (26%)	218
		Tamoxifen	65	50	15 (23%)	168
	> 65	Anastrozole	76	43	33 (43%)	461
		Tamoxifen	85	63	22 (26%)	199

Table 32: Reviewer's analysis of TTP by age group

Population	Analysis (Tamoxifen: anastrozole)	Age	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	≤ 65	1.32	0.96	(0.90, 1.92)	0.15
		> 65	1.65	1.24	(1.17, 2.33)	0.004
	Unadjusted ^c	≤ 65	1.30	0.95	(0.90, 1.89)	0.17
		> 65	1.56	1.17	(1.11, 2.18)	0.01
PP	Adjusted	≤ 65	1.46	1.02	(0.95, 2.25)	0.09
		> 65	1.74	1.25	(1.17, 2.59)	0.006
	Unadjusted	≤ 65	1.40	0.99	(0.92, 2.13)	0.11
		> 65	1.64	1.18	(1.11, 2.43)	0.01

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] time to disease progression than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H₀: hazard ratio = 1 against H₁: hazard ratio ≠ 1.

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Figure 19: Reviewer's Kaplan-Meier probability of TTP using ITT population (age ≤ 65)

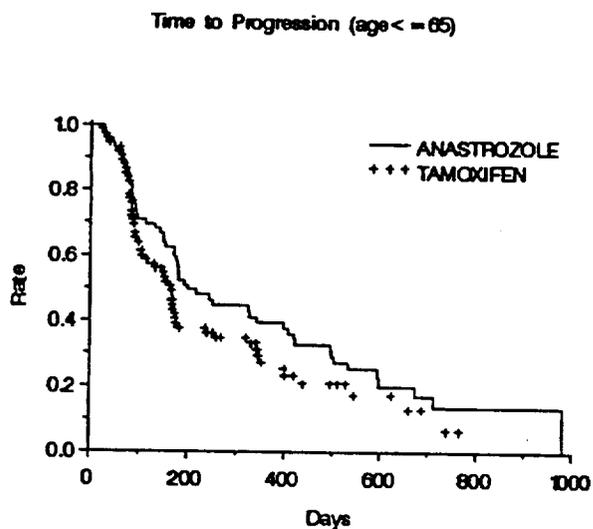


Figure 20: Reviewer's Kaplan-Meier probability of TTP using ITT population (age > 65)

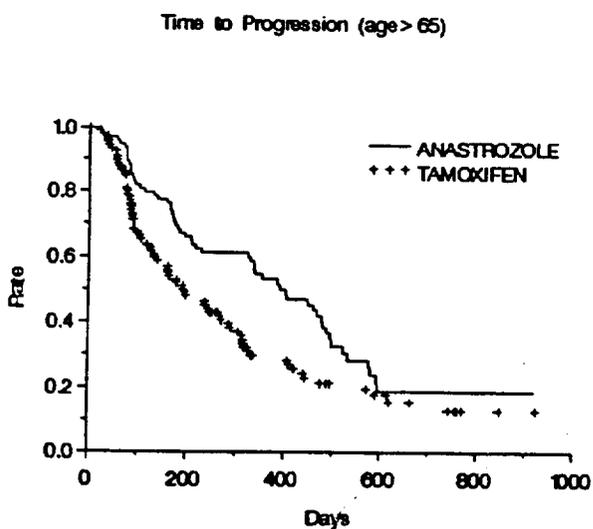


Figure 21: Reviewer's Kaplan-Meier probability of TTP using PP population (age ≤ 65)

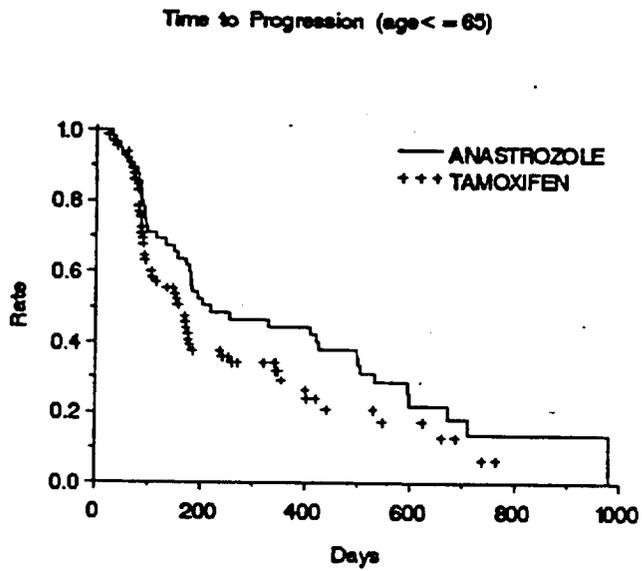
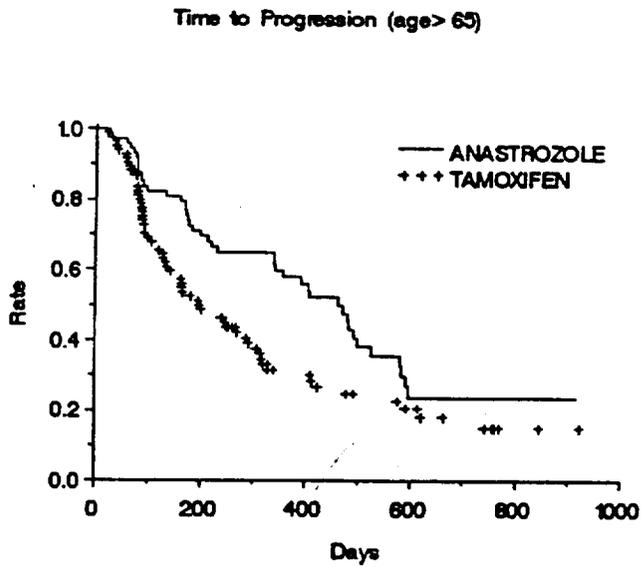


Figure 22: Reviewer's Kaplan-Meier probability of TTP using PP population (age > 65)



5.2.2.2 Objective response Rate

Table 33: Reviewer's descriptive summary of objective response by age group

Population	Age	Treatment	N	Responses (%)	Difference in response rate (anastrozole-tamoxifen)
ITT	≤ 65	Anastrozole	74	13 (18%)	1.78%
		Tamoxifen	76	12 (16%)	
	> 65	Anastrozole	97	23 (24%)	5.79%
		Tamoxifen	106	19 (18%)	
PP	≤ 65	Anastrozole	57	10 (18%)	2.16%
		Tamoxifen	65	10 (15%)	
	> 65	Anastrozole	76	19 (25%)	5.00%
		Tamoxifen	85	17 (20%)	

Table 34: Reviewer's analysis of objective response by age group

Population	Age	Difference in response rate (anastrozole - tamoxifen)	One-sided lower 95% CL	Two-sided 95% CI	P-value ^a
ITT	≤ 65	1.78%	-9.57%	(-11.49%, 15.04%)	0.942
	> 65	5.79%	-4.58%	(-6.38%, 17.95%)	0.400
PP	≤ 65	2.16%	-10.57%	(-12.69%, 17.01%)	0.939
	> 65	5.00%	-7.09%	(-9.17%, 19.17%)	0.569

^a Based on a two-sided test for H_0 : difference in response rate = 0 against H_1 : difference \neq 0.

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5.2.2.3 Time to Death (Survival)

Table 35: Reviewer's descriptive summary of survival by age group

Population	Age	Treatment	N	Failed	Censored	Median time to death (days)
ITT	≤ 65	Anastrozole	74	27	47 (64%)	980
		Tamoxifen	76	28	48 (63%)	979
	> 65	Anastrozole	97	97	61 (63%)	952
		Tamoxifen	106	106	59 (56%)	921
PP	≤ 65	Anastrozole	57	19	38 (67%)	NA
		Tamoxifen	65	23	42 (65%)	979
	> 65	Anastrozole	76	24	52 (68%)	952
		Tamoxifen	85	38	47 (55%)	921

Table 36: Reviewer's analysis of survival by age group

Population	Analysis (Tamoxifen: anastrozole)	Age	Hazard ratio ^a	One-sided lower 95% CL	Two-sided 95% CI	P-value ^d
ITT	Adjusted ^b	≤ 65	1.08	0.68	(0.63, 1.85)	0.79
		> 65	1.13	0.77	(0.71, 1.73)	0.64
	Unadjusted ^c	≤ 65	1.06	0.68	(0.62, 1.82)	0.82
		> 65	1.08	0.75	(0.69, 1.67)	0.74
PP	Adjusted	≤ 65	1.14	0.67	(0.61, 2.13)	0.69
		> 65	1.39	0.90	(0.82, 2.34)	0.22
	Unadjusted	≤ 65	1.12	0.66	(0.60, 2.06)	0.73
		> 65	1.33	0.86	(0.79, 2.22)	0.28

^a Hazard ratios of greater [less] than 1.00 indicate that anastrozole was associated with a longer [shorter] survival time than was tamoxifen.

^b The adjusted analysis was performed using a Cox regression model including factors of treatment, age, previous adjuvant hormonal therapy, oestrogen/progesterone receptor status, and extent of disease at entry.

^c The unadjusted analysis was performed using a Cox regression model including treatment factor only.

^d Based on a two-sided test for H₀: hazard ratio = 1 against H₁: hazard ratio ≠ 1.

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Figure 23: Reviewer's Kaplan-Meier probability of survival using ITT population (age ≤ 65)

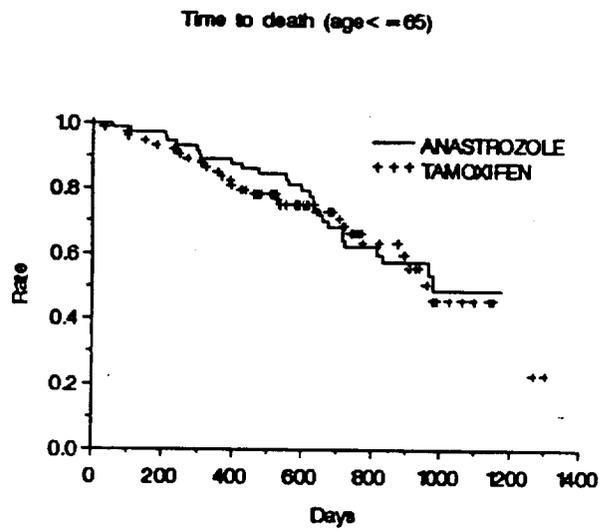


Figure 24: Reviewer's Kaplan-Meier probability of survival using ITT population (age > 65)

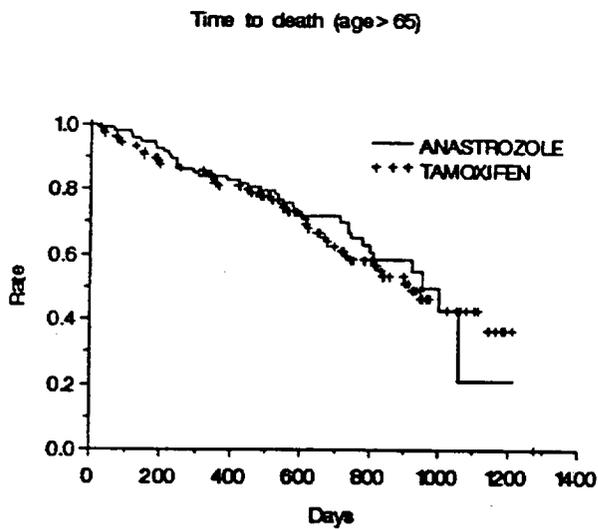


Figure 25: Reviewer's Kaplan-Meier probability of survival time using PP population (age ≤ 65)

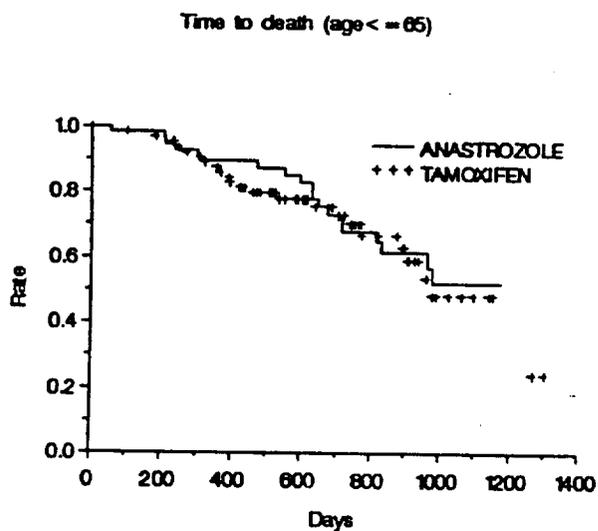
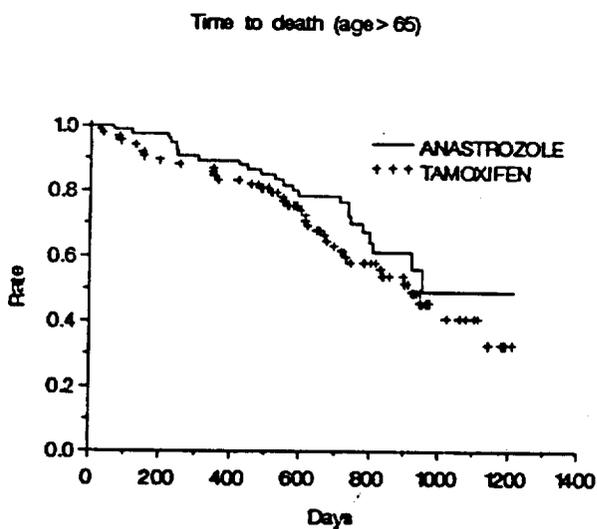


Figure 26: Reviewer's Kaplan-Meier probability of survival time using PP population (age > 65)



/S/

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Mathematical Statistician

Concur: Dr. Chen

/S/

8/24/00

Dr. Chi

8/24/00

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This review consists of 53 pages of text.