

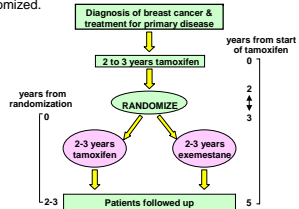
## INTRODUCTION

The IES is an inter co-operative group, randomized, double-blind, phase 3 trial in postmenopausal women with early breast cancer. Patients disease free after 2-3 yrs tamoxifen were randomized to continue tamoxifen or switch to exemestane for a further 2-3 yrs to complete 5 yrs adjuvant endocrine therapy.

Tamoxifen induces uterine abnormalities detectable by ultrasound e.g. endometrial thickening, in postmenopausal women. The effects of switching to an anti-aromatase agent such as exemestane are not known, yet the IES study which reported earlier this year (NEJM 2004; 350: 1081-92) provides an ideal opportunity to evaluate this. Preliminary results of the IES Endometrial Sub-protocol, in which a subgroup of patients underwent detailed endometrial assessments, are reported.

## IES STUDY DESIGN

4740 patients with ER positive/unknown, histologically or cytologically confirmed, completely resected, adequately treated unilateral adenocarcinoma of the breast were randomized.



## STUDY DESIGN – Endometrial Sub-protocol

All patients from a subset of centers were considered.

### Eligibility criteria included:

- intact uterus
- no previous endometrial cancer or other uterine malignancy
- no undiagnosed vaginal bleeding within the past 12 months.

### Primary endpoint:

proportion of patients with endometrial thickness  $\geq 5$ mm after 2 yrs of randomized treatment.

### Secondary endpoints:

- transvaginal ultrasound changes including mean endometrial thickness, mean uterine volume, presence of polyps, fibroids, ovarian cysts.
- histological & immunohistochemical findings in patients who undergo biopsy or hysterectomy.

## METHODS

Transvaginal ultrasound examinations were performed at randomization & at 6, 12 & 24 months to assess:

- Endometrial thickness (ET) (independently reviewed)
- Uterine volume
- Uterine diameter
- Other uterine findings

These evaluations were to be repeated 1 & 2 years after treatment completion.

## STATISTICAL CONSIDERATIONS

**Planned sample size:** 176 patients (200 allowing for a 15% attrition rate) were required to detect a 25% difference in the proportion of patients with endometrial thickening (ET $\geq 5$ mm) (assuming 55% in the tamoxifen arm & 30% in the exemestane arm) with 90% power, 5% two-sided significance.

**Statistical methods:** The primary endpoint was analyzed using a chi-squared test. Within group changes in ET & uterine volume from baseline were analyzed as secondary endpoints using paired t-tests. Between group comparisons used two-sample t-tests & descriptive tables. All analyses used a 5% significance level & were performed by intention to treat.

**Statistical power in this analysis:** Following publication of main trial results, it was decided to analyse & release available data from each sub-protocol. At this time, the complete treated case subset of 90 patients provides 67% power.

## PATIENT POPULATION

219 randomized patients were entered into the endometrial sub-protocol. Analyses were conducted on the snapshot of data comprising all data received relating to visits to 30<sup>th</sup> June 2003. Two analysis subsets are considered here:

- 180 patients** with endometrial assessments performed within windows of +/- 1 month of 6 & 12 month follow-ups, & +/- 2 months of 24 month follow-up. These assessment windows are in accordance with the protocol & provided 179 patients at baseline (1 patient-missing data on baseline ET), 137 at 6 months, 121 at 12 months & 96 at 24 months. This is an "all available data" analysis.

- 90 patients** who had received at least 2 yrs randomized treatment & had an on-treatment ultrasound performed between 22 & 26 months from treatment start. This is a "treated & complete case" analysis.

36 patients were entered from a single centre & have not been included in this analysis as it has not been possible to verify the reliability of data. 3 patients were not included as they have no assessment data available.

## RESULTS

### Baseline Results:

Baseline patient characteristics were well balanced between the treatment arms in both analysis populations (Table 1).

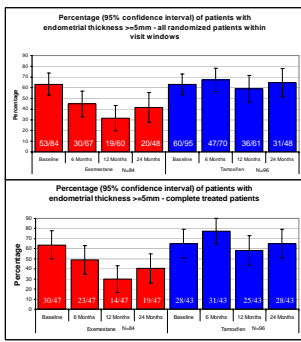
Table 1 Baseline patient & tumour characteristics

Exemestane N=84		Tamoxifen N=96		Exemestane N=47		Tamoxifen N=43	
%	%	%	%	%	%	%	%
23.8	19.8	<55	23.4	14.0			
20.2	22.9	65-69	19.1	25.6			
22.6	18.8	60-64	17.0	20.9			
16.7	25.0	65-69	19.1	30.2			
16.7	13.5	70+	21.3	9.3			
82.1	68.8	Positive	80.9	67.4			
11.9	9.4	Negative	8.5	14.0			
6.0	11.9	Unknown/Missing	10.6	18.6			
41.7	44.8	Positive	42.6	44.2			
16.7	12.5	Negative	17.0	11.6			
41.7	42.7	Unknown	40.4	44.2			
75.0	66.7	Mastectomy	83.0	67.4			
25.0	33.3	BCT	17.0	32.6			
16.7	11.5	Yes	19.1	14.0			
48.8	52.1	Yes	44.7	39.5			

Most patients had not had endometrial ultrasound during pre-randomization tamoxifen treatment & of those who had, the majority were assessed as normal. 11/84 patients in the exemestane group & 14/96 in the tamoxifen group reported at least one abnormality. 12 patients in each group had undergone investigations other than endometrial ultrasound

### Abnormal Endometrial Thicknesses During the Study:

Figure 2a,b Percentage (95% CI) of patients with ET $\geq 5$ mm



Figures 2a & 2b show the proportion (95% CI) of patients with endometrial thickness  $\geq 5$ mm at each assessment. Numbers of patients are also shown.

Thus, in randomized patients within the visit windows, the proportion with ET $\geq 5$ mm at the 24 month follow-up visit is 41.7% [95% CI: 27.8% to 55.6%] in the exemestane group & 64.6% [95% CI: 51.5% to 77.7%] in the tamoxifen group, (p=0.024). Differences in the proportion with ET $\geq 5$ mm were also seen at 6 & 12 months (p=0.008 & 0.003 respectively).

Similarly, for treated complete cases, the proportion with ET $\geq 5$ mm at 24 months is 40.4% [95% CI: 26.4% to 54.4%] in the exemestane arm & 65.1% [95% CI: 50.9% to 79.3%] in the tamoxifen arm, (p=0.019).

Table 2: Normalized ET at 24 Months (randomized patients within the visit windows)

Endometrial thickness at baseline	Endometrial thickness at 24 month follow-up			
	Exemestane (N=84)		Tamoxifen (N=96)	
	<5mm	$\geq 5$ mm	<5mm	$\geq 5$ mm
<5mm	13 (76.5%)	4 (23.5%)	11 (61.1%)	7 (34.9%)
$\geq 5$ mm	15 (48.4%)	16 (16.6%)	6 (20.0%)	24 (80.0%)

In patients with an abnormal ET at baseline (i.e.  $\geq 5$ mm), 15 patients in the exemestane arm (48.4%) & 6 patients in the tamoxifen arm (20.0%) had a normal ET (i.e.  $< 5$ mm) at 24 months. A similar effect was also seen for treated complete cases, with 15 patients in the exemestane group (50.0%) & 6 patients in the tamoxifen group (21.4%) having a normal endometrial thickness after 2 years of treatment.

### Comparison of Mean ET and Uterine Volumes:

At 6 months, a significant change in ET was seen within the exemestane group (mean change -1.75mm, 95% CI: -2.95 to -0.56, p=0.005) but not in the tamoxifen group (Table 3). The comparison of mean change was significant at 6 months (mean difference -1.70mm; 95% CI: -3.05 to -0.35, p=0.014). Mean uterine volume was also significantly reduced at 6 months in patients switching to exemestane (mean change -15.5cm<sup>3</sup>, 95% CI: -23.40 to -7.51, p=0.0002) while remaining similar in the tamoxifen group (Table 4).

Table 3 Difference in ET (mm) from baseline

All available	Exemestane				Tamoxifen			
	Baseline	6 months	12 months	24 months	Baseline	6 months	12 months	24 months
	n	n	n	n	n	n	n	n
Mean	2.24	2.48	4.58	5.14	7.45	6.63	6.20	7.14
Mean change from baseline	-	-0.24	-2.10	-2.66	-1.18	-0.15	-0.62	-0.46
Complete case analysis	-	-1.75	-2.24	-2.42	-	-0.05	-0.30	-0.13
Mean change from baseline	-	-1.75	-2.24	-2.42	-	-0.05	-0.30	-0.13
95% CI	-	(-3.05, -0.45)	(-3.59, -0.89)	(-3.91, -1.93)	-	(-0.97, -0.03)	(-1.21, -0.51)	(-1.21, -0.46)

\* p < 0.001, \*\* p < 0.01, \*\*\* p < 0.005

Figure 3a,b Mean change (95% CI) in ET from baseline

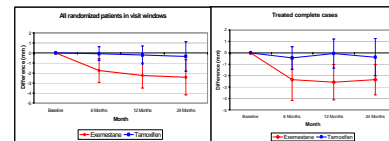


Table 4 Difference in Uterine Volume in cm<sup>3</sup> from baseline

All available	Exemestane				Tamoxifen			
	Baseline	6 months	12 months	24 months	Baseline	6 months	12 months	24 months
	n	n	n	n	n	n	n	n
Mean	46.0	32.0	27.0	28.7	48.6	50.6	46.5	52.0
Mean change from baseline	-	-15.1	-20.5	-20.7	-	-1.4	-1.1	1.2
Complete case analysis	-	-15.1	-20.5	-20.7	-	-1.4	-1.1	1.2
Mean change from baseline	-	-15.1	-20.5	-20.7	-	-1.4	-1.1	1.2
95% CI	-	(-23.4, -6.8)	(-28.5, -12.5)	(-28.9, -12.5)	-	(-6.6, -0.2)	(-6.2, -0.2)	(-5.6, 3.2)

## CONCLUSIONS

- After two years of randomized treatment, the proportion of patients with ET $\geq 5$ mm was significantly reduced in patients switching to exemestane
- A significant reduction in ET & uterine volume was observed at 6 months in the exemestane group, & although the thickness continued to decrease, no further significant changes were observed
- Switching to exemestane allows reversal of sub-clinical uterine abnormalities associated with tamoxifen
- Further follow-up will allow a more complete analysis of endometrial changes whilst on treatment (to 24 months)
- Information on post-treatment changes is still required. Assessments at 1 & 2 yrs after completion of randomized treatment will elucidate this.

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