

# **INTERGROUP EXEMESTANE STUDY**

## **Updated survival analysis**

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**A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen**

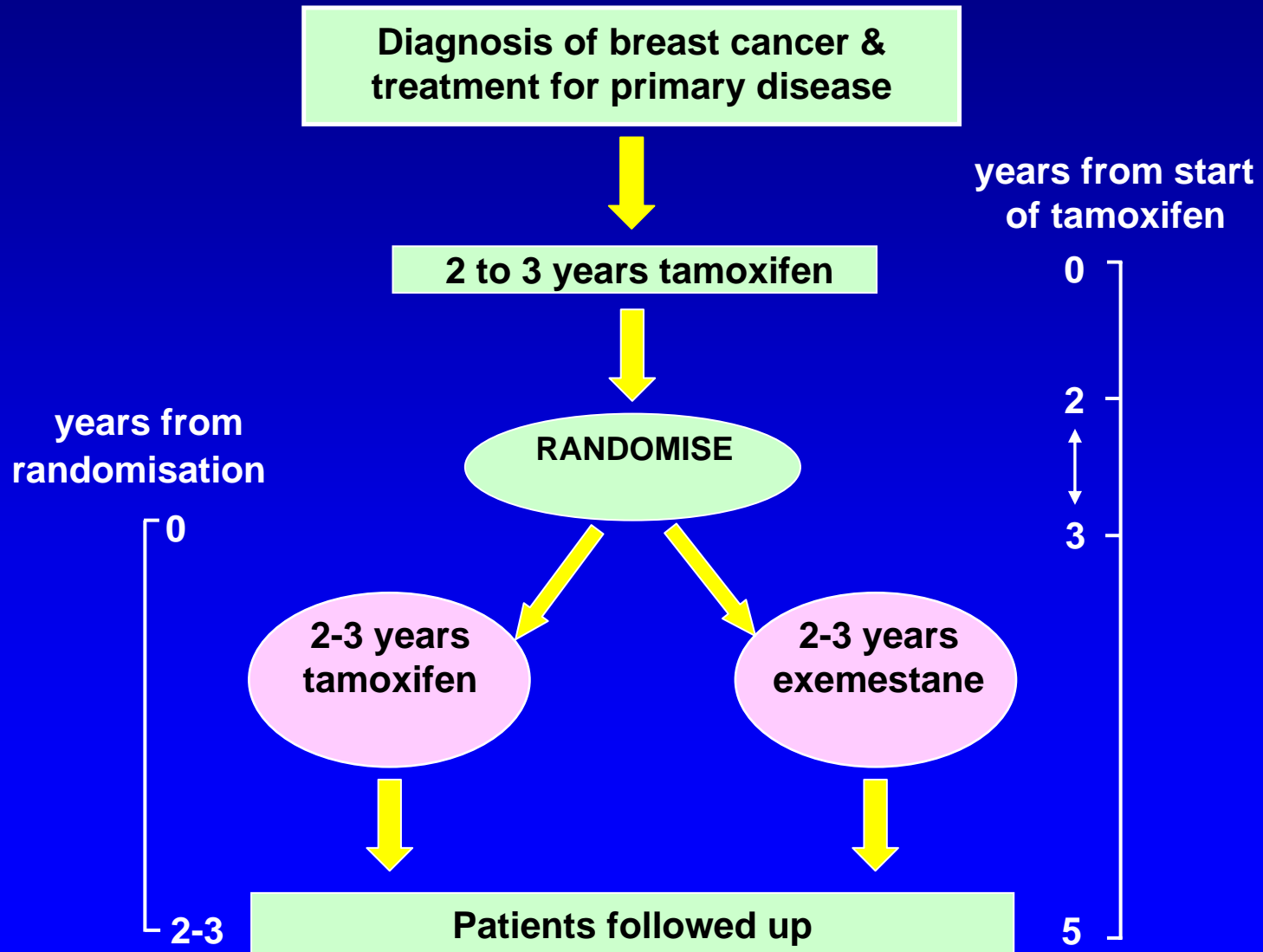
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**ABCG, ANZBCTG, CEEOG, DBCG, EORTC, FNCLCC, GEAG, GEICAM, GOIRC,  
GONO, IBCSG, ICOG, ITMO, NBCG, NWEG, SBCG, US Onc, WCTN, YBG**

**Breast International Group (BIG)**



# IES: STUDY DESIGN



# IES: PRIMARY END POINT

## ➤ Disease-free survival (DFS)

defined as time from randomization to:

- breast cancer recurrence
- contralateral breast cancer (2<sup>nd</sup> primary)
- intercurrent deaths (death from any cause, prior to breast cancer recurrence)

**Time to recurrence = excludes intercurrent deaths & 2<sup>nd</sup> primary BC**

# IES: SECONDARY END POINTS

- Overall survival
- Incidence of contralateral breast cancer
- Long-term safety/tolerability
- Sub-studies investigating
  - Uterine thickening
  - Bone mineral density and bone metabolism
  - Quality of life

# IES: DEMOGRAPHICS I

	Exemestane	Tamoxifen
<b>Number of patients *</b>	<b>2352</b>	<b>2372</b>
<b>Median age, n (range)</b>	<b>63.0 (38.0-96.0)</b>	<b>63.0 (31.0-90.0)</b>
<b>Nodal Status, n (% known)</b>		
<b>Negative</b>	<b>1217 (54)</b>	<b>1228 (54)</b>
<b>Positive</b>	<b>1048 (46)</b>	<b>1038 (46)</b>
<b>Prior Chemotherapy, n (%)</b>		
<b>Yes</b>	<b>774 (33)</b>	<b>769 (32)</b>
<b>No</b>	<b>1578 (67)</b>	<b>1603 (68)</b>

\* Of the 4742 subjects included in the NEJM analysis, 2 were found to have duplicate PIDs and 16 subjects from one center were excluded from all analyses because data were considered unreliable.

# IES: DEMOGRAPHICS II

	<b>Exemestane (n=2352)</b>	<b>Tamoxifen (n=2372)</b>
<b>Receptor Status, n (%)</b>		
<b>ER &amp; PgR Positive</b>	<b>1331 (56.6)</b>	<b>1319 (55.6)</b>
<b>ER Positive &amp; PgR Negative/Unknown</b>	<b>677 (28.8)</b>	<b>692 (29.2)</b>
<b>ER and PgR Unknown</b>	<b>288 (12.2)</b>	<b>291 (12.3)</b>
<b>ER Negative</b>	<b>54 (2.3)</b>	<b>65 (2.7)</b>
<b>Median duration of Tamoxifen treatment (mths) at time of randomisation</b>	<b>28.5</b>	<b>28.4</b>

# IES: EFFICACY ANALYSIS

	NEJM	Current analysis
<b>DFS events</b>	<b>449</b>	<b>615</b>
<b>Deaths</b>	<b>199</b>	<b>339</b>
<b>Median Follow-up</b>	<b>30.6 months</b>	<b>37.4 months</b>

# IES: EVENTS CONTRIBUTING TO DISEASE FREE SURVIVAL

	Exemestane	Tamoxifen	Total
Local recurrence only†	43	56	99
Distant recurrence	150	208	358
Contralateral breast primary	12	26	38
Intercurrent deaths (without recurrence)	57	63	120
<b>Total number of patients experiencing an event</b>	<b>262</b>	<b>353</b>	<b>615</b>

† Includes 1 ipsilateral breast cancer

# IES: CAUSES OF DEATH

Exemestane Tamoxifen Total

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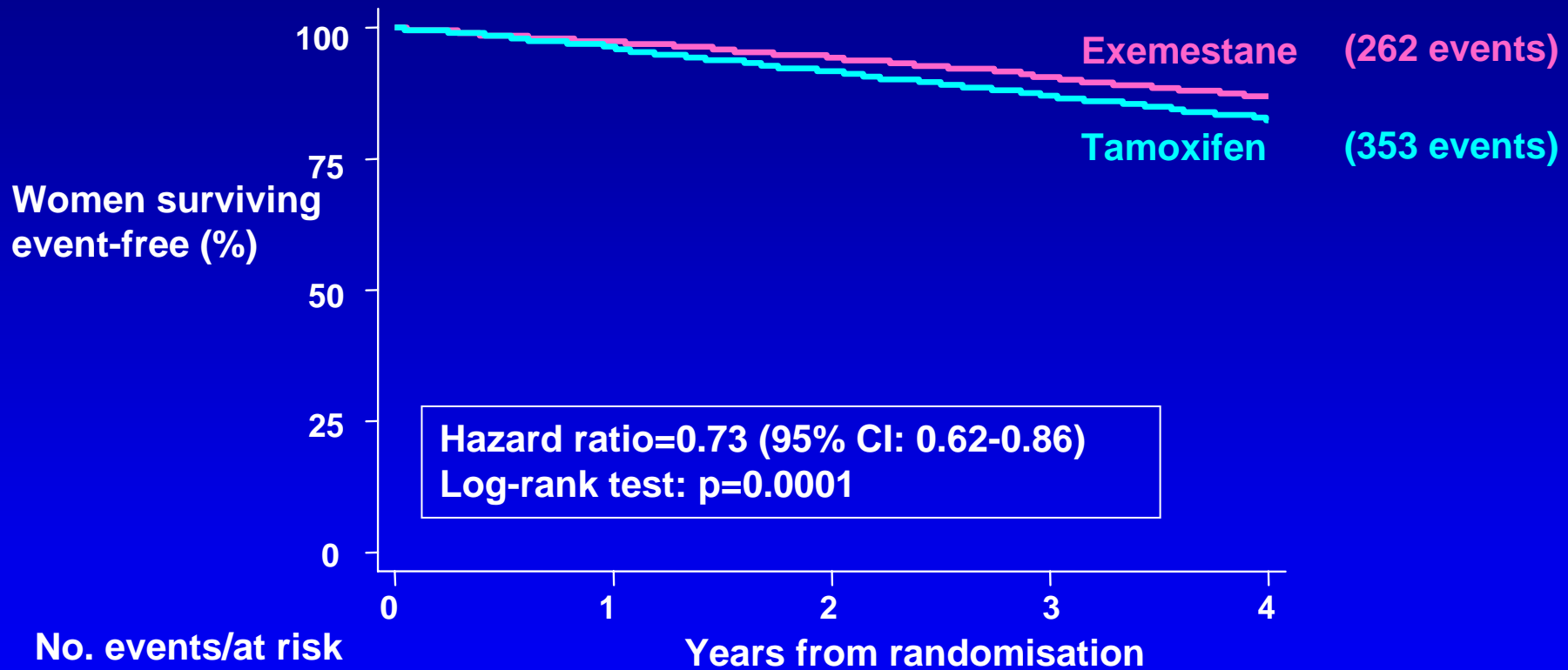
<b>Total number of deaths</b>	<b>152</b>	<b>187</b>	<b>339</b>
<b>Breast cancer deaths</b>	<b>95</b>	<b>124</b>	<b>219</b>
Inc. other COD in patients with recurrence/CLB	11	12	23
<b>Intercurrent (without recurrence/CLB)</b>	<b>57</b>	<b>63</b>	<b>120</b>
Vascular	15	7	22
Cardiac	13	12	25
Other cancer	13	22	35
Other	11	14	25
Unknown	5	8	13

# IES: DISEASE FREE SURVIVAL

	Hazard Ratio	95 % CI*	P value
Disease free survival	0.73	0.62-0.86	0.0001
Time to recurrence	0.70	0.58-0.83	0.00005
Time to contralateral breast cancer	0.50	0.26-0.97	0.04

\* CI denotes confidence interval

# IES: DISEASE FREE SURVIVAL

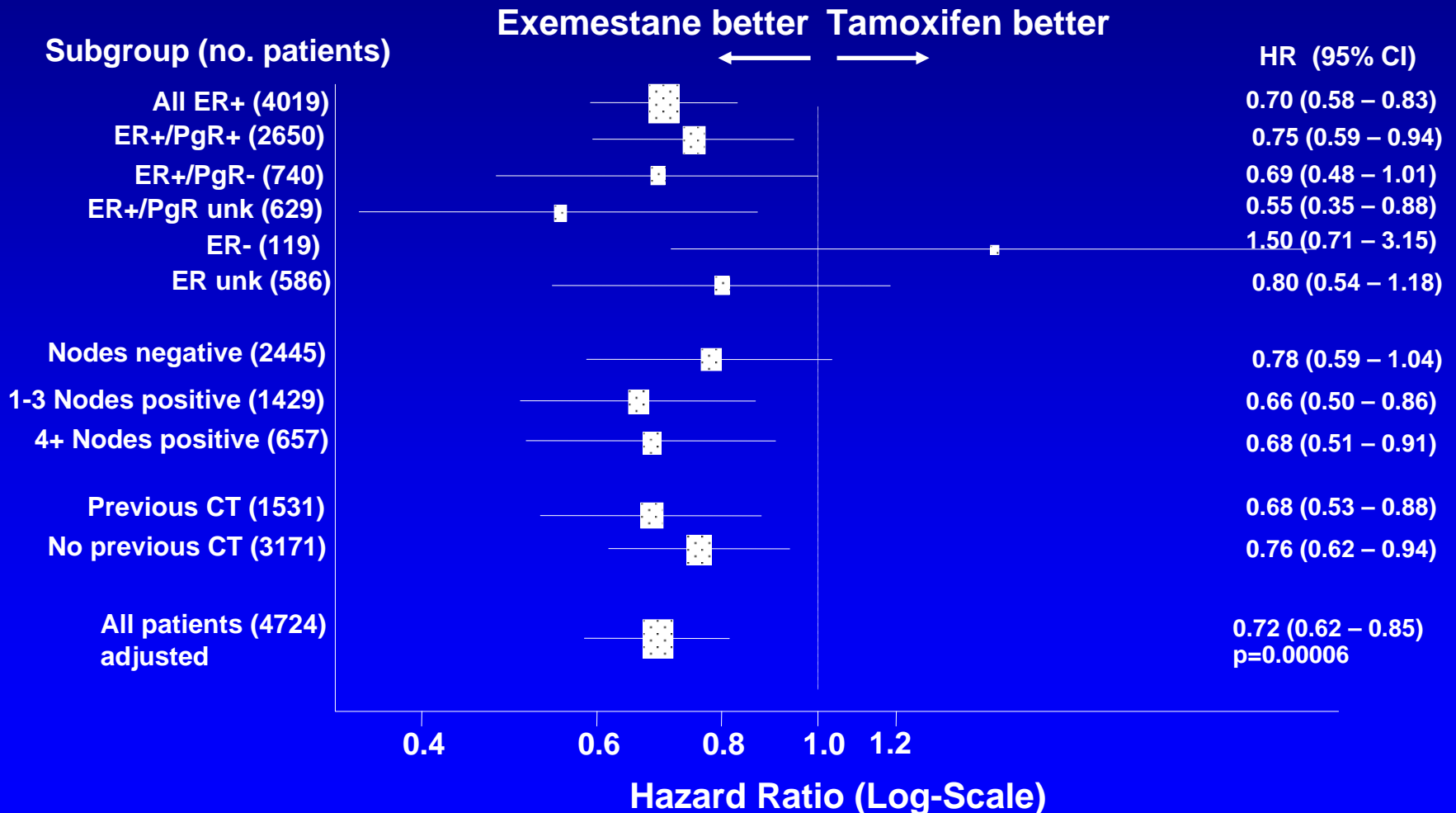


<b>Exemestane</b>	<b>0 / 2352</b>	<b>57 / 2233</b>	<b>65 / 2081</b>	<b>75 / 1413</b>	<b>41+24<sup>†</sup> / 661</b>
<b>Tamoxifen</b>	<b>0 / 2372</b>	<b>82 / 2243</b>	<b>105 / 2062</b>	<b>96 / 1359</b>	<b>47+23<sup>†</sup> / 650</b>

<sup>†</sup> events occurring more than 4 years after randomisation

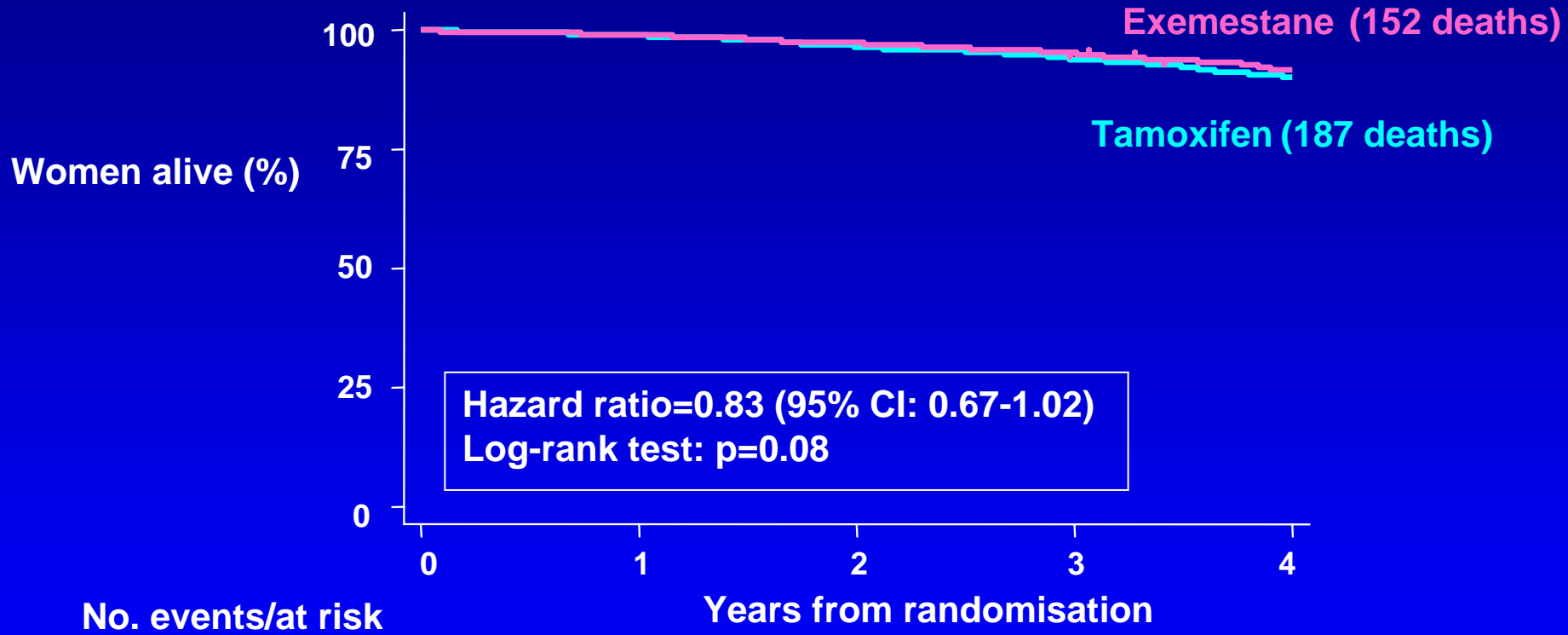
# IES: DISEASE FREE SURVIVAL

## Subgroup Analysis



Data are hazard ratios (HR) and 95% confidence intervals (CI)

# IES: OVERALL SURVIVAL



Exemestane	0 / 2352	18 / 2270	41 / 2137	41 / 1469	37+15 <sup>†</sup> / 690
Tamoxifen	0 / 2372	23 / 2300	53 / 2165	49 / 1465	41+21 <sup>†</sup> / 701

<sup>†</sup> events occurring more than 4 years after randomisation

# IES: SITES OF OTHER CANCERS

	Exemestane	Tamoxifen
<b>Total non-breast 2<sup>nd</sup> primaries</b>	<b>46</b>	<b>69</b>
Uterus	6	14
GI	13	16
Lung	6	13
Melanoma	2	5
Ovary	4	1
Other	15	20

# IES: PREVIOUS MEDICAL HISTORY (6 months prior to study entry)

	Exemestane (N=2352)	Tamoxifen (N=2372)
Disorders (MedDRA SOC term)	N (%)	N (%)
<b>Any</b>	<b>1294 (55.0)</b>	<b>1292 (54.5)</b>
Cardiovascular (inc hypertension)	775 (32.9)	729 (30.7)
Musculoskeletal & connective tissue	287 (12.2)	289 (12.2)
Metabolism & nutrition	238 (10.1)	258 (10.9)
Psychiatric	145 (6.2)	124 (5.2)
Endocrine	134 (5.7)	136 (5.7)

Occurring in > 5 % of patients in either treatment arm

# IES: SAFETY PROFILE

Data: Adverse events / Illnesses up to 30/06/03

Coding: MedDRA

## Incident case analysis (IC)

Population: ITT

Timeframe: All follow-up visits

Criteria: Any event

## Treatment emergent (TE)

Population: As treated

Timeframe: On treatment + 30 days

Criteria: New or more severe events (as compared with baseline)

**Presentation of events where difference between treatment groups (in either IC or TE analysis)  $p < 0.01$**

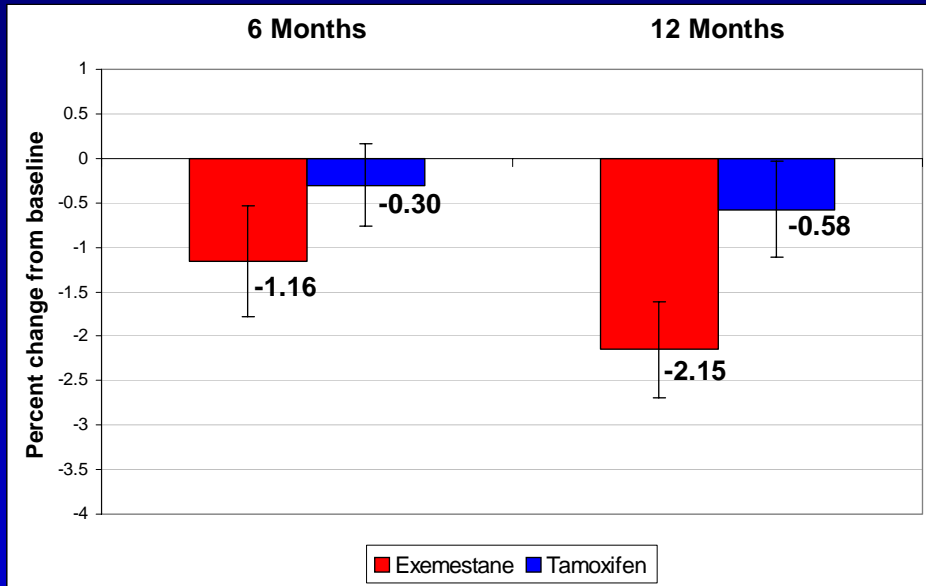
+ trend test; NS = Non-significant ( $p \geq 0.01$ ), \*  $0.001 \leq p < 0.01$ , \*\*  $p \leq 0.001$

# IES: SAFETY PROFILE: Musculoskeletal - 1

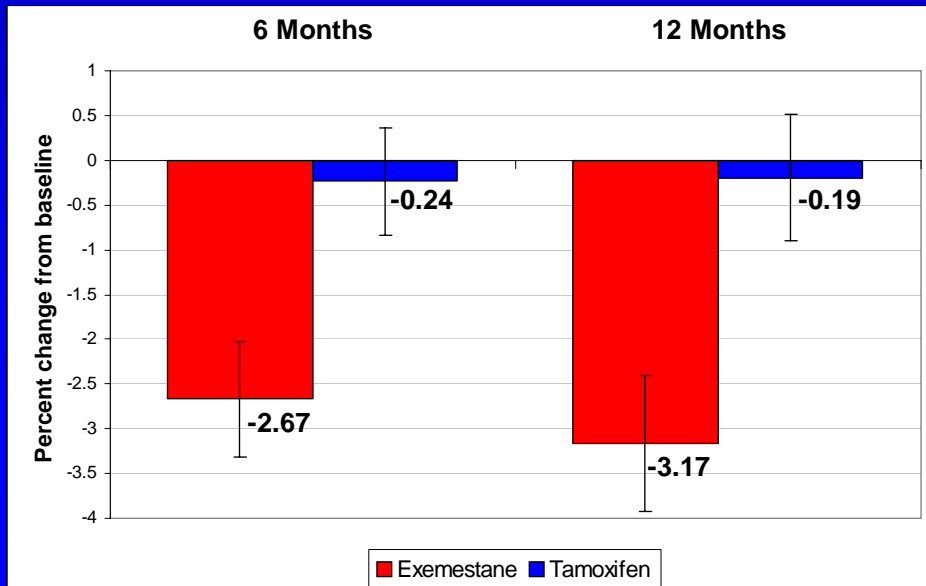
Incidence Case Analysis				
Events	Exemestane n (%)	Tamoxifen n (%)	<i>P</i>	<i>Treatment emergent</i> <i>P</i>
Any Grade				
Osteoporosis	175 (8.3)	145 (6.9)	NS (0.08)	*

**NB No significant excess of fractures at present**

# IES: BONE SUB-PROTOCOL N = 206



← Percent change in total hip BMD



← Percent change in lumbar spine BMD

Graphs show mean and 95% CI

# **IES: BONE SUB-PROTOCOL CONCLUSIONS**

- **Tamoxifen protection lost rapidly – differences in BMD seen <6m of switching to exemestane**
- **Decrease in BMD at 6m could be due to dual effects of tamoxifen withdrawal & treatment with exemestane**
- **BMD loss in patients who switched to exemestane appears similar to other AIs at 2-3% in first year of therapy**
- **2 yr data will inform whether rate of BMD change with exemestane arm is less once confounding effect of tamoxifen withdrawal has passed**

# IES: SAFETY PROFILE: Musculoskeletal - 2

Events	Incidence Case Analysis			<i>Treatment emergent P</i>
	Exemestane n (%)	Tamoxifen n (%)	<i>P</i>	
Any Grade				
Arthralgia	417 (19.8)	275 (13.1)	<0.001+	**
Myalgia	50 (2.4)	32 (1.5)	0.004+	NS
Arthritis / osteoarthritis	354 (16.8)	285 (13.5)	0.003	Osteo NS
Muscle cramp	64 (3.0)	107 (5.1)	0.001+	**
Pain in limb	260 (12.3)	206 (9.8)	NS (0.01)	*
Carpal tunnel	57 (2.7)	8 (0.4)	<0.001	**
Paraesthesia	69 (3.3)	29 (1.4)	<0.001+	**

# IES: SAFETY PROFILE: Thrombo-embolic Disease

Events Any Grade	Incidence Case Analysis			Treatment emergent <i>P</i>
	Exemestane n (%)	Tamoxifen n (%)	<i>P</i>	
Thrombo-embolic disease	41 (1.9)	69 (3.3)	<0.001+	*

# IES: SAFETY PROFILE: Myocardial Infarction

Events	Incidence Case Analysis			Treatment emergent P
	Exemestane n (%)	Tamoxifen n (%)	P	
Any Grade				
Myocardial Infarction (MI) (Fatal + Non Fatal)				
All MIs	20 (0.9)	8 (0.4)	NS (0.02)	
Age (mean)	68.8	70.9		
On treatment MIs	14 (0.7)	7 (0.3)	NS (0.13)	NS
All patients with MI had $\geq 1$ predisposing risk factor				

## Tamoxifen: association with MI

- Meta-analysis: Braithwaite et al, 2003: 52,929 patients.
- ?? Decrease in incidence of MI (HR 0.74 (0.47-1.16))
- Decreases death from MI (HR 0.55 (0.36-0.87))

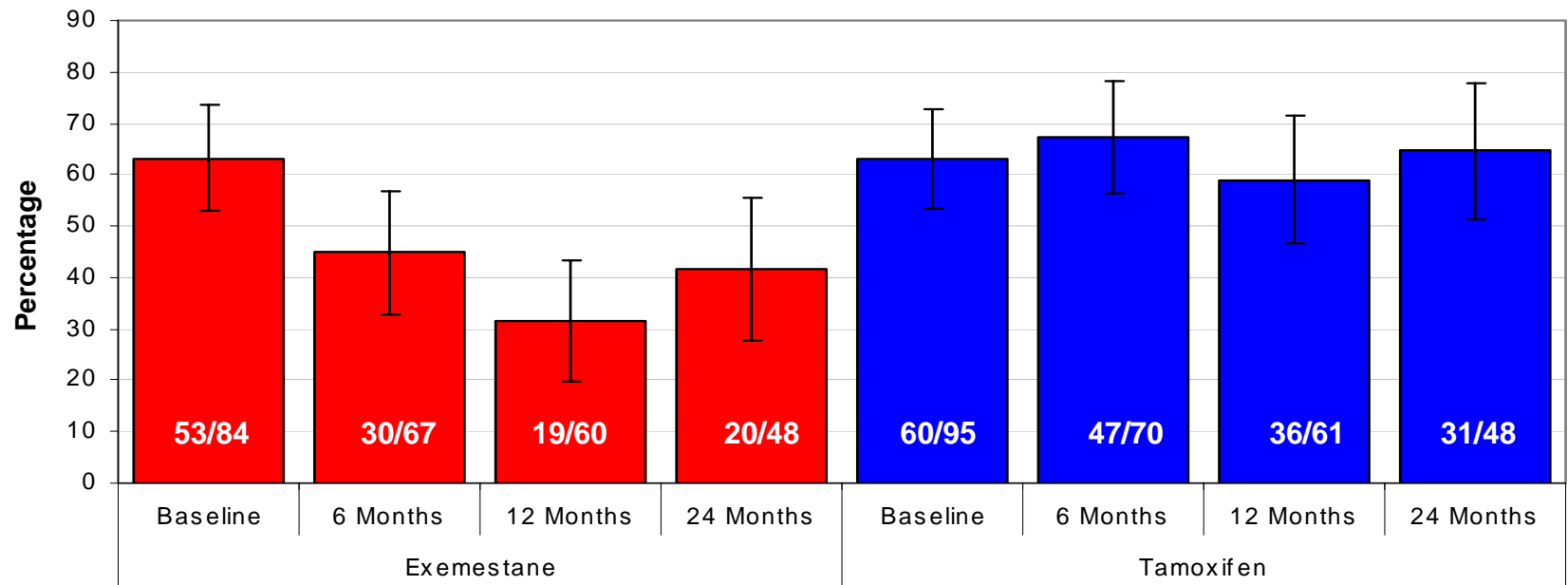
**RE-CHECKING /  
CLARIFICATION  
OF CV EVENTS  
ONGOING**

# IES: SAFETY PROFILE: Gynaecological

Incidence Case Analysis				
Events	Exemestane	Tamoxife	<i>P</i>	<i>Treatment emergent</i>
Any Grade	n (%)	n n (%)		<i>P</i>
Gynecological symptoms	301 (14.3)	376 (17.8)	0.002	Not done
Uterine Hyperplasia	19 (0.9)	39 (1.9)	0.008	**
Uterine Polyps	12 (0.6)	53 (2.5)	<0.001	**

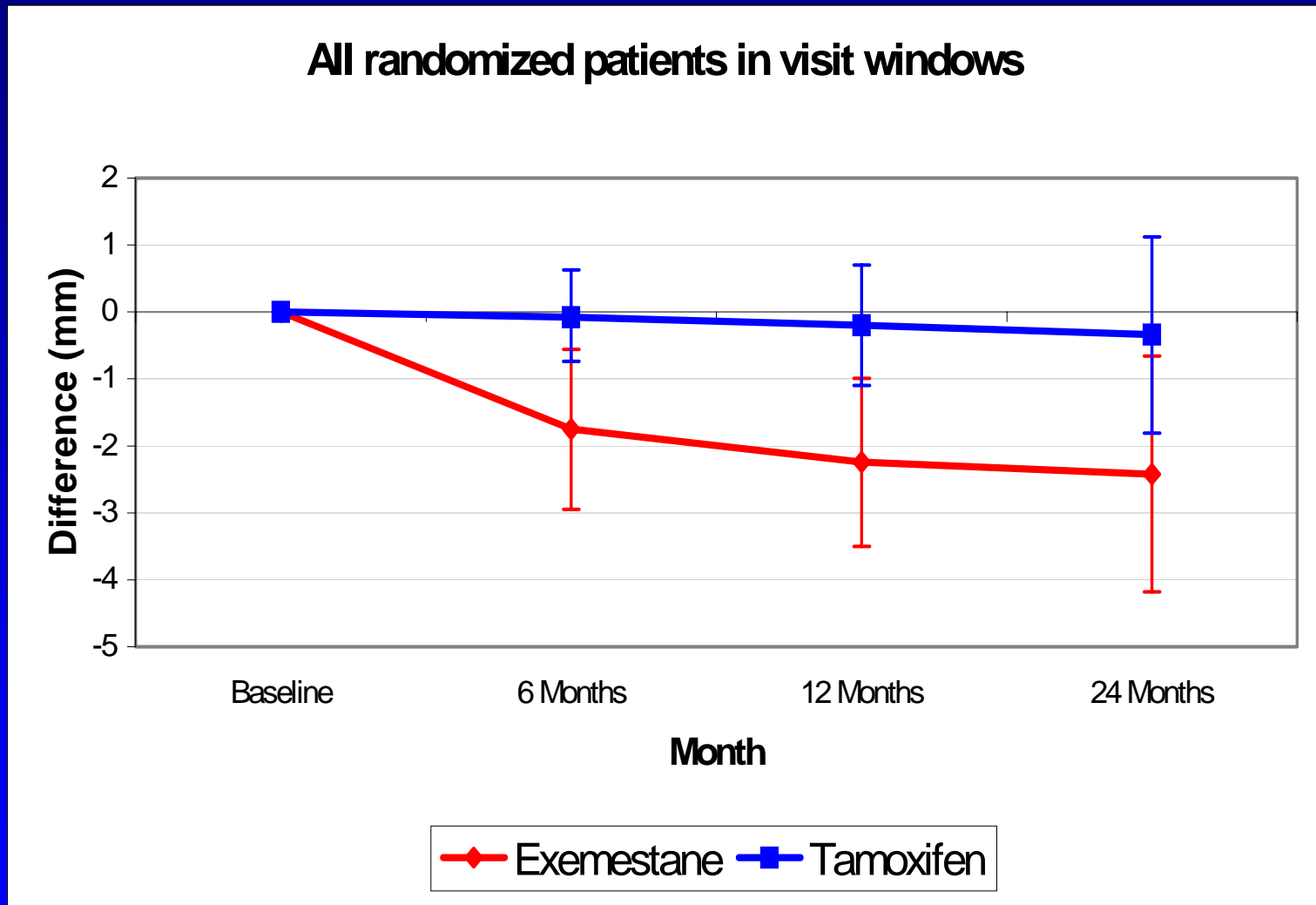
# IES: ENDOMETRIAL SUB-PROTOCOL (N= 180)

Percentage (95% confidence interval) of patients with endometrial thickness  $\geq 5\text{mm}$  - all randomized patients within visit windows



Difference at 24 months  $p=0.024$

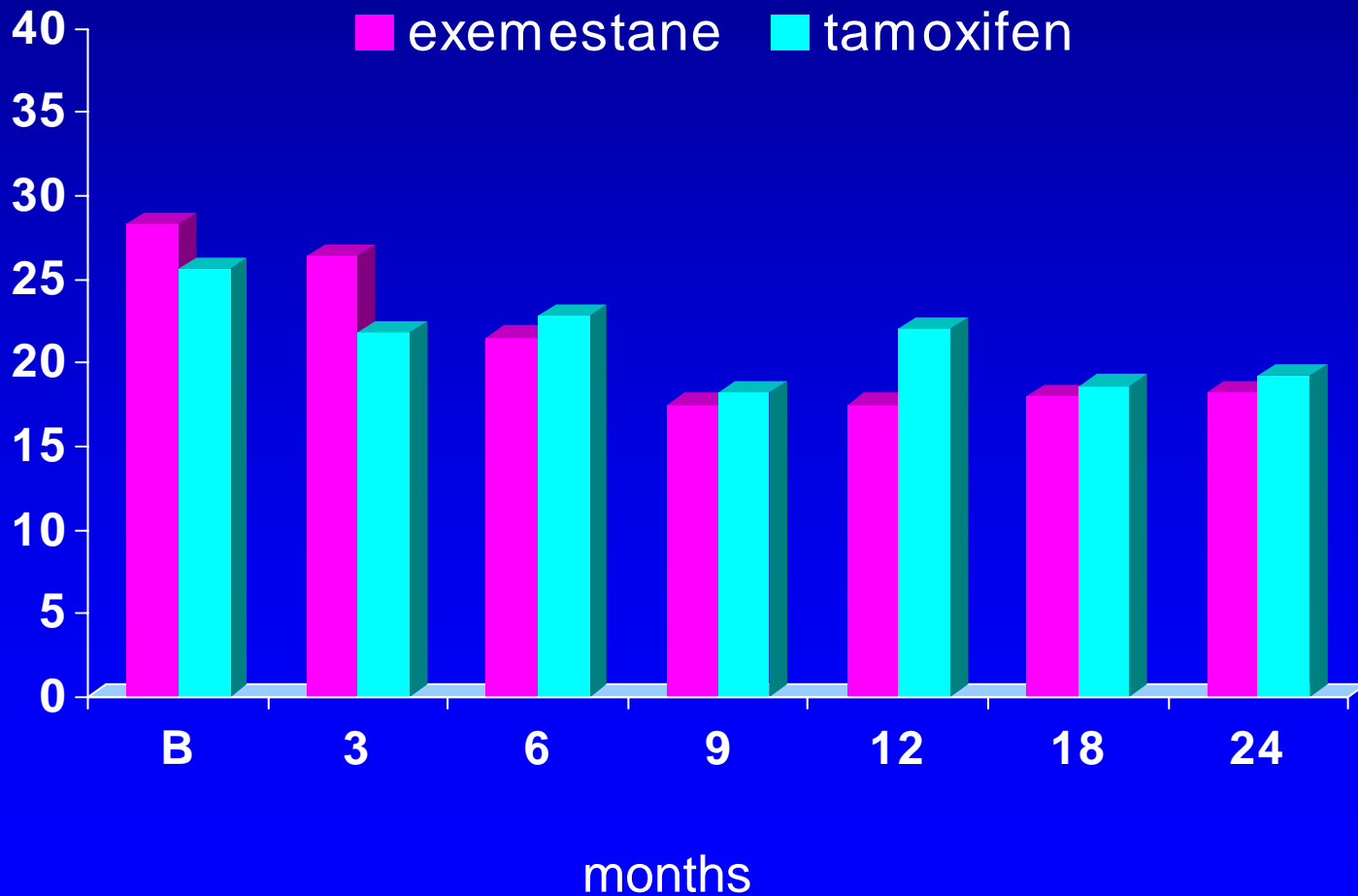
# IES: ENDOMETRIAL SUB-PROTOCOL (N= 180)



Mean change (95% CI) in ET from baseline

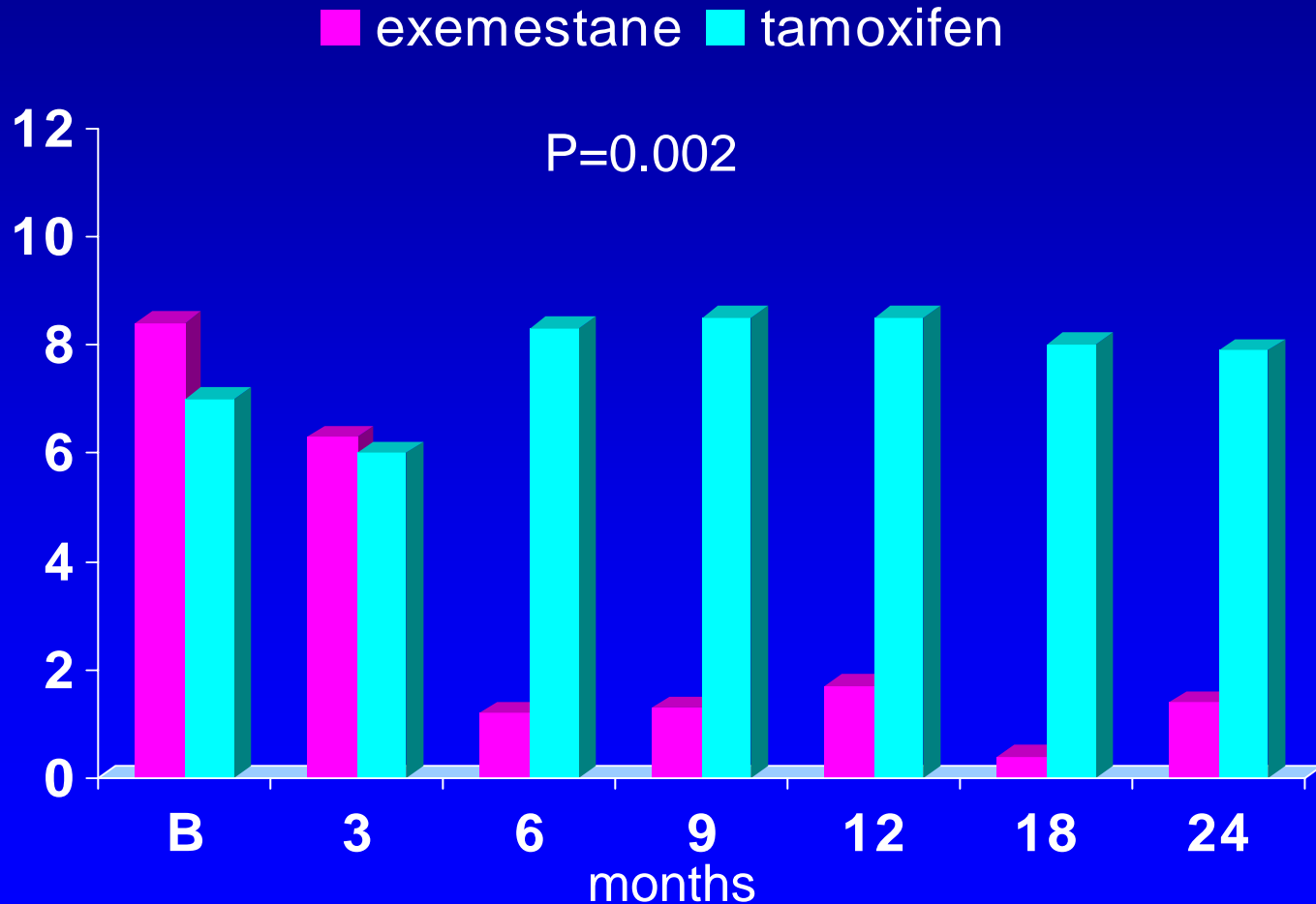
# QOL SUB-PROTOCOL (N=556)

## % patients with severe night sweats



# QOL SUB-PROTOCOL (N=556)

## % patients with severe vaginal discharge



# IES: SAFETY PROFILE: Other

	Incidence Case Analysis			
Events Any Grade	Exemestane n (%)	Tamoxifen n (%)	<i>P</i>	<i>Treatment emergent P</i>
<b>Also:</b>				
Diarrhoea	111 (5.3)	63 (3.0)	0.001+	**
Insomnia	474 (22.5)	423 (20.1)	NS (0.06)+	**

# **IES: SAFETY CONCLUSIONS**

- **No excess of intercurrent deaths**
- **Endocrine effects similar to tamoxifen**
- **Musculo-skeletal side effects more common**
- **Cardiovascular - more data required but serious events very rare**
- **Exemestane associated with a reduction in gynecological and thrombo-embolic side effects**

# IES: EFFICACY CONCLUSIONS

- **Switching to exemestane reduces the risk of:**
  - **breast cancer recurrence (p=0.0001)**
  - **contralateral breast cancer (p=0.04)**
- **Switching to exemestane appears to reduce the chances of dying (p=0.08) but more follow-up is needed**

# IES: ACKNOWLEDGEMENTS



Imperial College  
London



**The patients, doctors, nurses, data managers and  
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