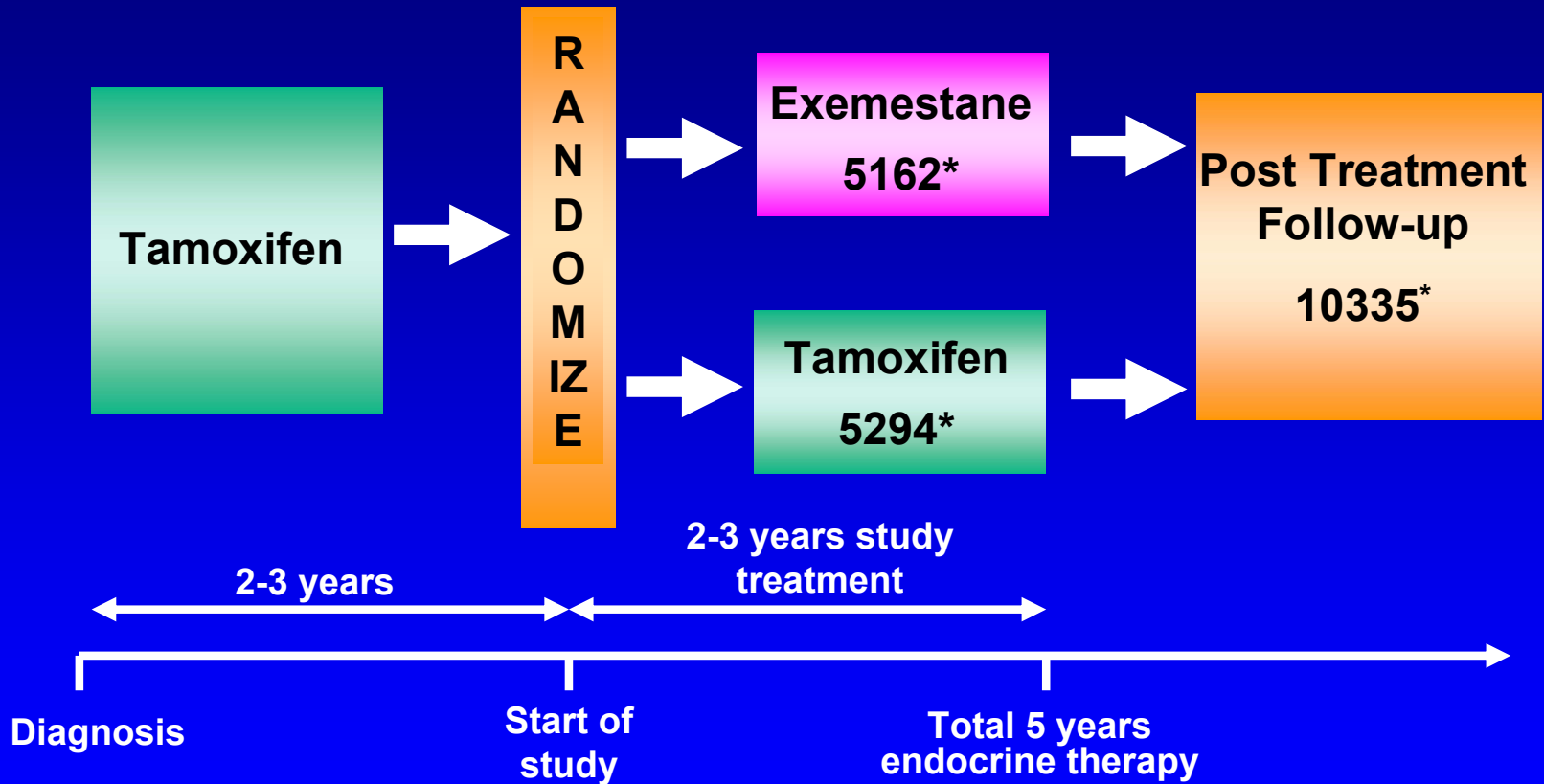


First Mature Analysis of the Intergroup Exemestane Study (IES)

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

Coombes RC, Paridaens R, Jassem J, Van De Velde CJH, Delozier T, Jones S, Hall E, Kilburn L, Snowdon CF and BLISS JM for the Intergroup Exemestane Study Investigators

Trial Design



* Total women years

4724 patients recruited from 366 sites in 37 countries between February 1998 & February 2003

20 collaborative groups worldwide



*Of the 4742 subjects included in the NEJM analysis, 2 had duplicate PIDs and 16 subjects from one centre were excluded because data were considered unreliable.

Study Endpoints - Definitions

Primary Endpoint

- Disease Free Survival (DFS)
 - breast cancer recurrence
 - contralateral breast cancer
 - intercurrent deaths

Secondary Endpoints

- Overall Survival (OS)
- Incidence of Contralateral Breast Cancer
- Long Term Tolerability & Safety

Additional Endpoints

- Breast Cancer Free Survival (BCFS)
- Time To Distant Recurrence (TTDR)

IES - Analyses

Date	March 2004	December 2004	June 2006
Where presented / published	NEJM*	SABCS**	ASCO
Triggered by	IDMC advised - stopping boundary for ½ required no. of events exceeded	More complete safety data & greater post-trt follow-up	IDMC & SC agreed – analyse at 95% ≥ 3 yrs FU & ER+/Unknown‡
Median FU in surviving patients	30.6 months	37.4 months	55.7 months
DFS Events	449	615	808
Deaths	199	339	483

‡ Excluding patients subsequently confirmed as ineligible due to ER negativity

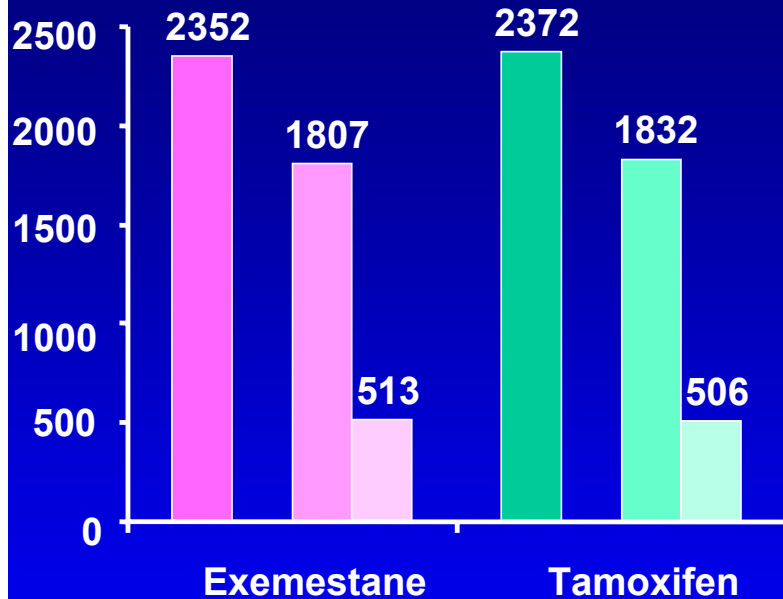
*Coombes RC et al. N Engl J Med 2004; Vol 350;11: 1081-1092.

**Coombes RC et al. Breast Cancer Res Treat 2004; Vol 88

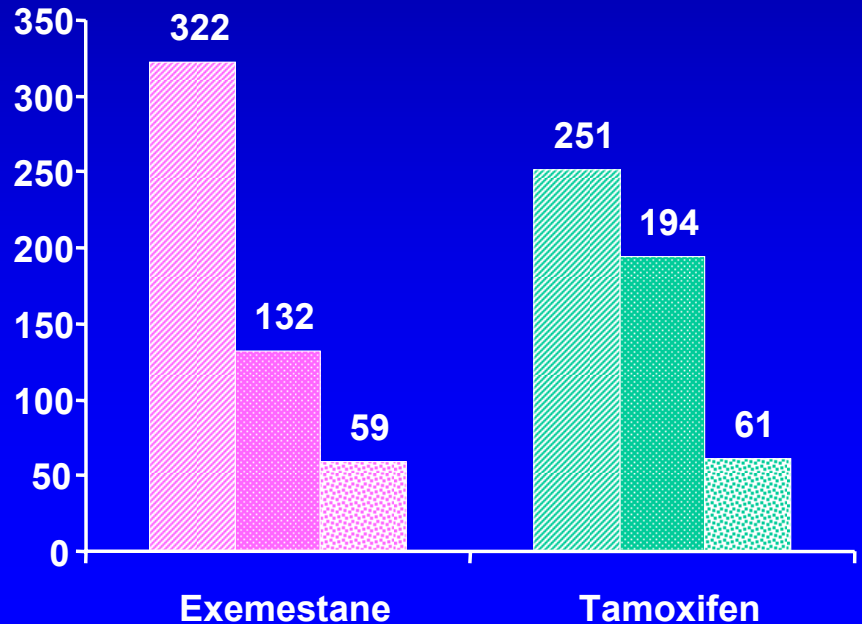
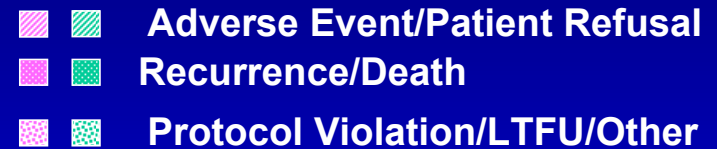
Demographics

	Exemestane (n = 2352)	Tamoxifen (n = 2372)
Median Age - Yrs, n (range)	63.9 (38.2 – 96.1)	63.8 (31.7 – 90.6)
Nodal Status	%	%
Negative	51.7	51.9
Positive	44.6	43.8
Missing/Unknown	3.7	4.3
Prior Chemotherapy		
Yes	32.9	32.4
No	67.1	67.6
Receptor Status		
ER+ & PR+	57.0	56.0
ER+ & PR-/Unknown	29.0	29.2
ER & PR Unknown	11.7	12.0
ER - (n = 122)	2.4	2.8

Patient Disposition/Compliance



Reasons for withdrawing

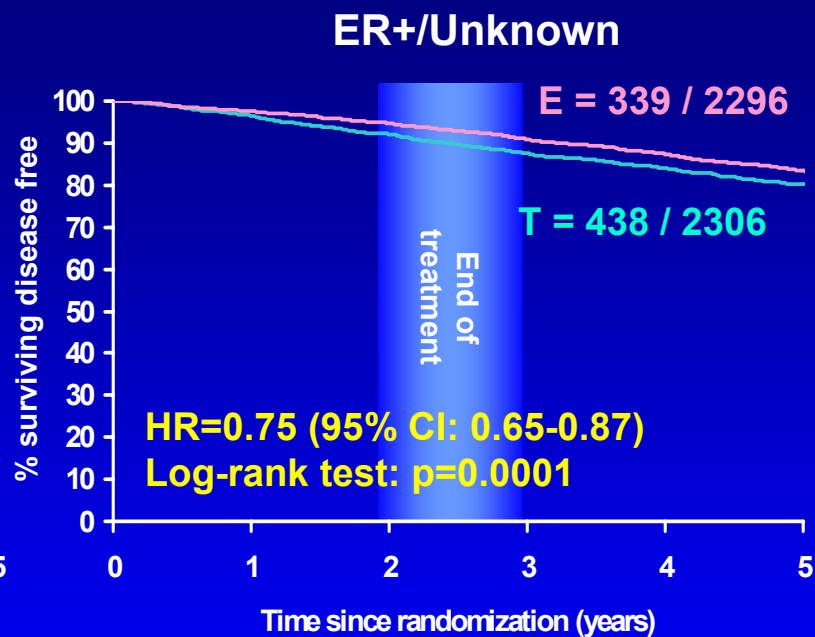
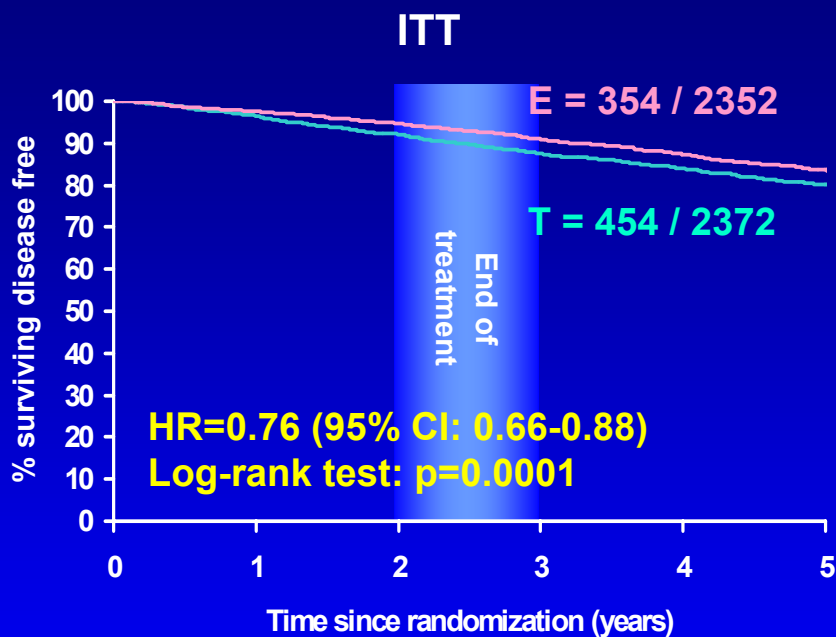


Efficacy Analysis

Events Contributing to DFS

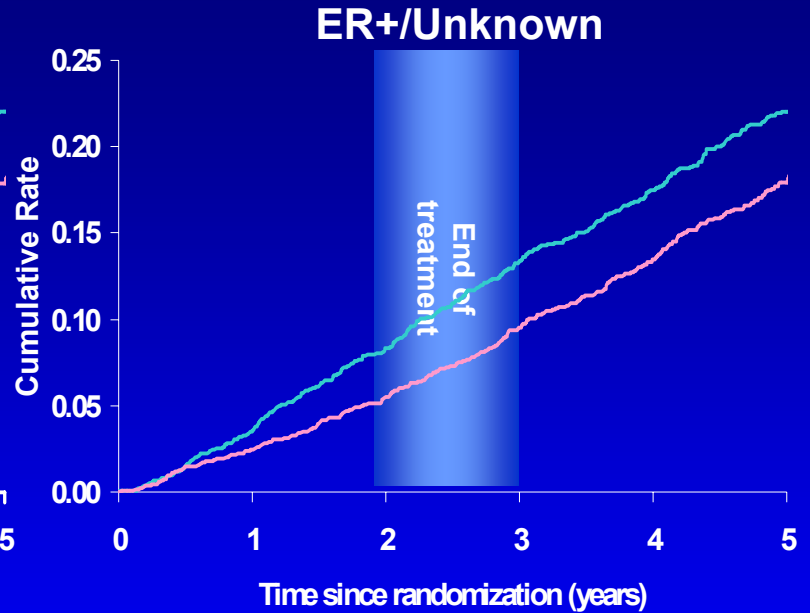
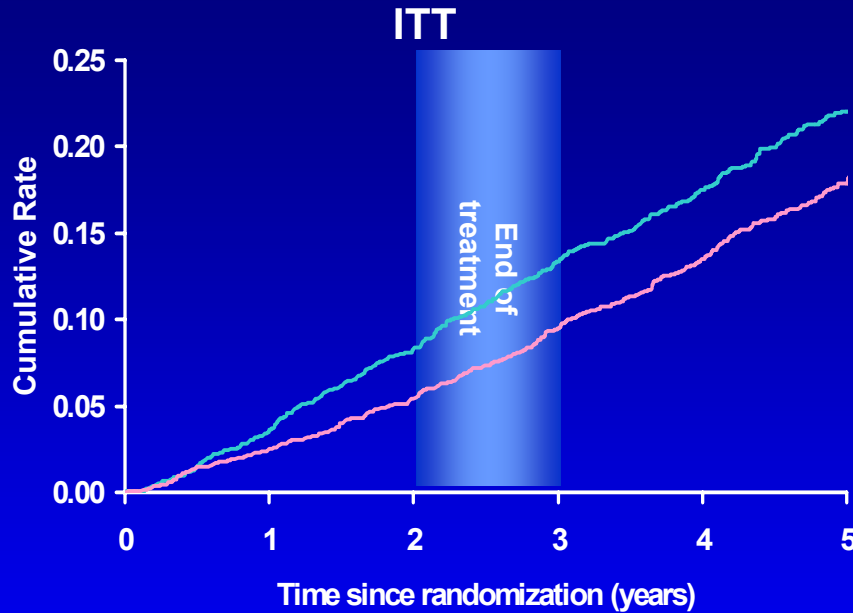
	Exemestane	Tamoxifen	Total
Distant recurrence	214	256	470
Local recurrence only	49	68	117
Contralateral breast primary	18	35	53
Intercurrent deaths	73	95	168
Total first events	354	454	808

Disease Free Survival



year	2.5	5	2.5	5
% abs. diff.	3.2	3.4	3.4	3.5
(95% CI)	(1.6 – 4.9)	(0.1 – 6.8)	(1.8 – 5.1)	(0.1 – 6.9)

Cumulative Hazard Rate – DFS



— Exemestane — Tamoxifen

Annual Hazard Rate, % (95% CI)

ITT	1	2	3	4	5
Exemestane	2.5 (1.9, 3.2)	3.0 (2.3, 3.8)	4.1 (3.3, 5.0)	4.0 (3.1, 5.0)	4.4 (3.4, 5.9)
Tamoxifen	3.6 (2.9, 4.4)	4.7 (3.9, 5.8)	5.0 (4.1, 6.1)	4.2 (3.3, 5.3)	4.6 (3.4, 6.0)

Disease Free Survival – Subgroups

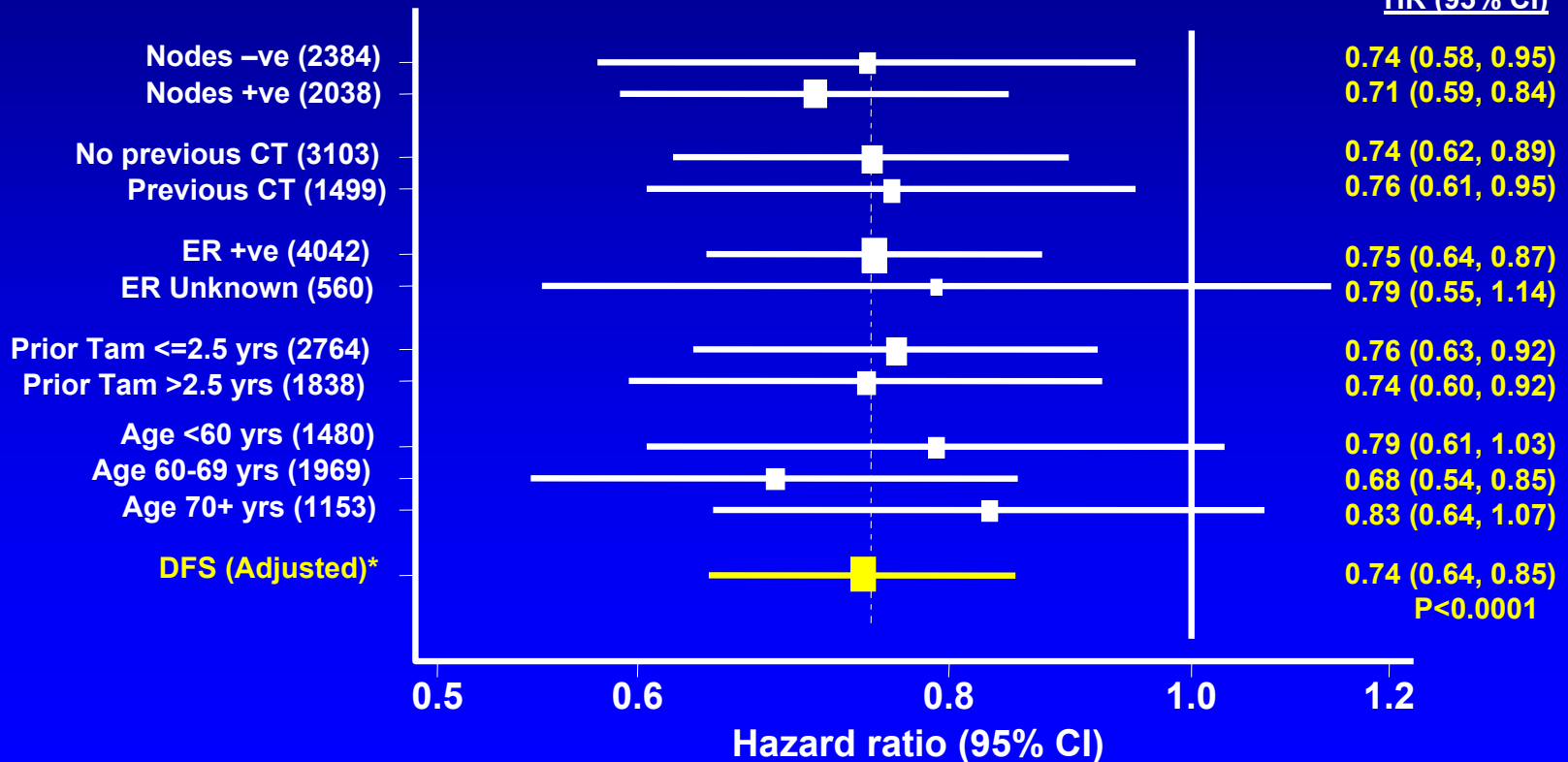
ER+/Unknown

Favors Exemestane

Favors Tamoxifen



HR (95% CI)



* Adjusted for Nodal Status, Chemotherapy Use & HRT Use

Efficacy Endpoints

Favors Exemestane

Favors Tamoxifen



HR (95%CI)

Disease Free Survival

ITT (E=354, T=454)

ER+/UNK (E=339, T=438)

Breast Cancer Free Survival

ITT (E=289, T=374)

ER+/UNK (E=277, T=361)

Time to Distant Recurrence

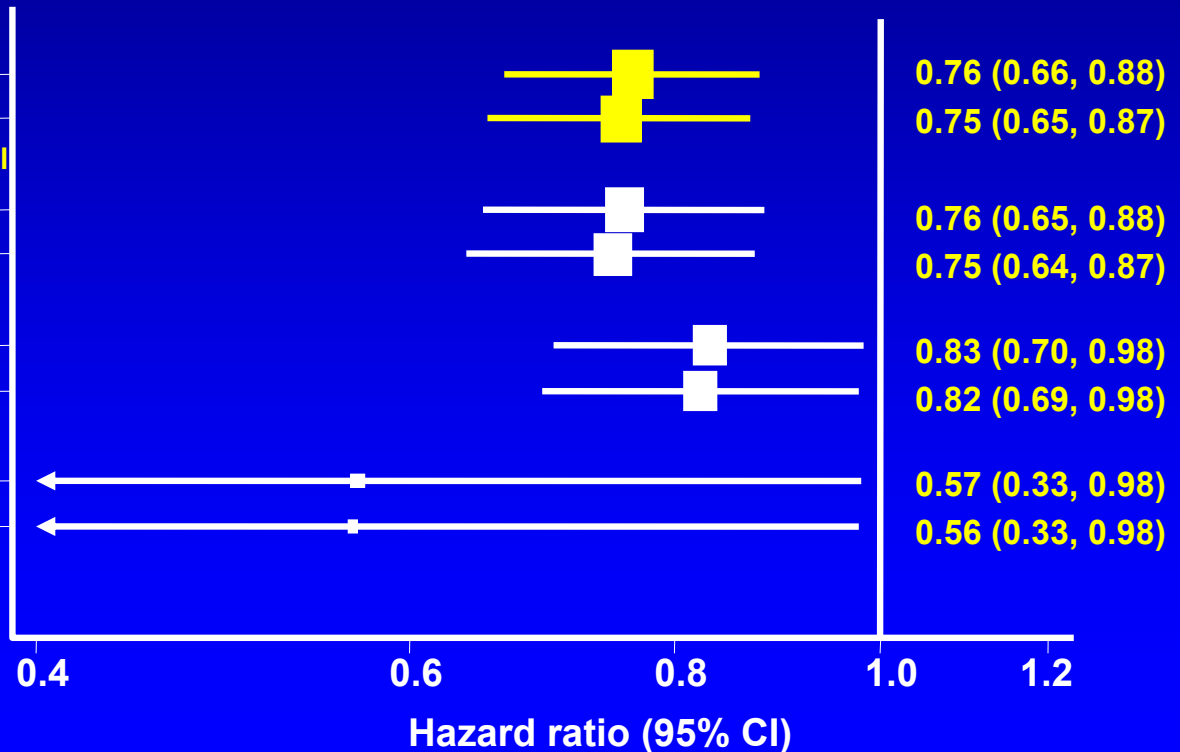
ITT (E=249, T=297)

ER+/UNK (E=238, T=285)

Time to Contralateral BC

ITT (E=20, T=35)

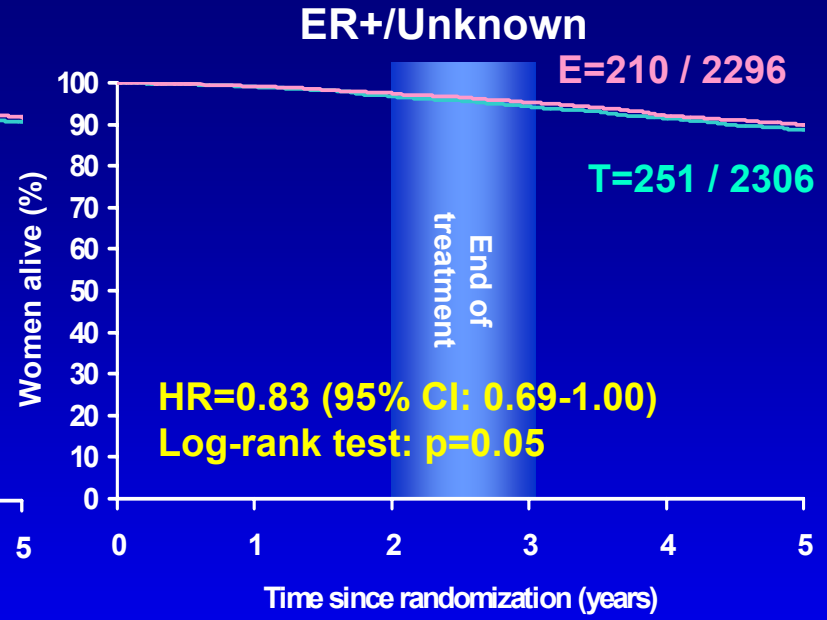
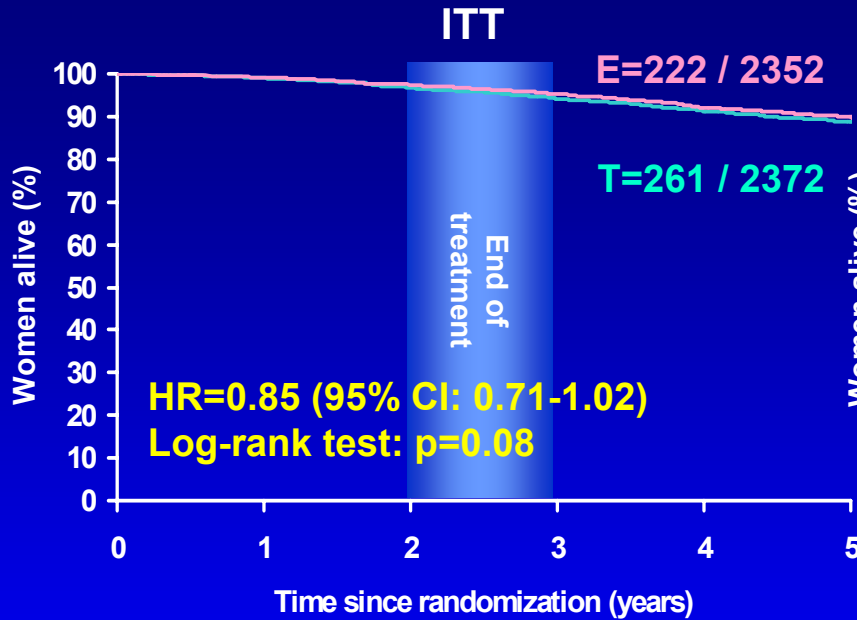
ER+/UNK (E=20, T=35)



Causes of Death - ITT

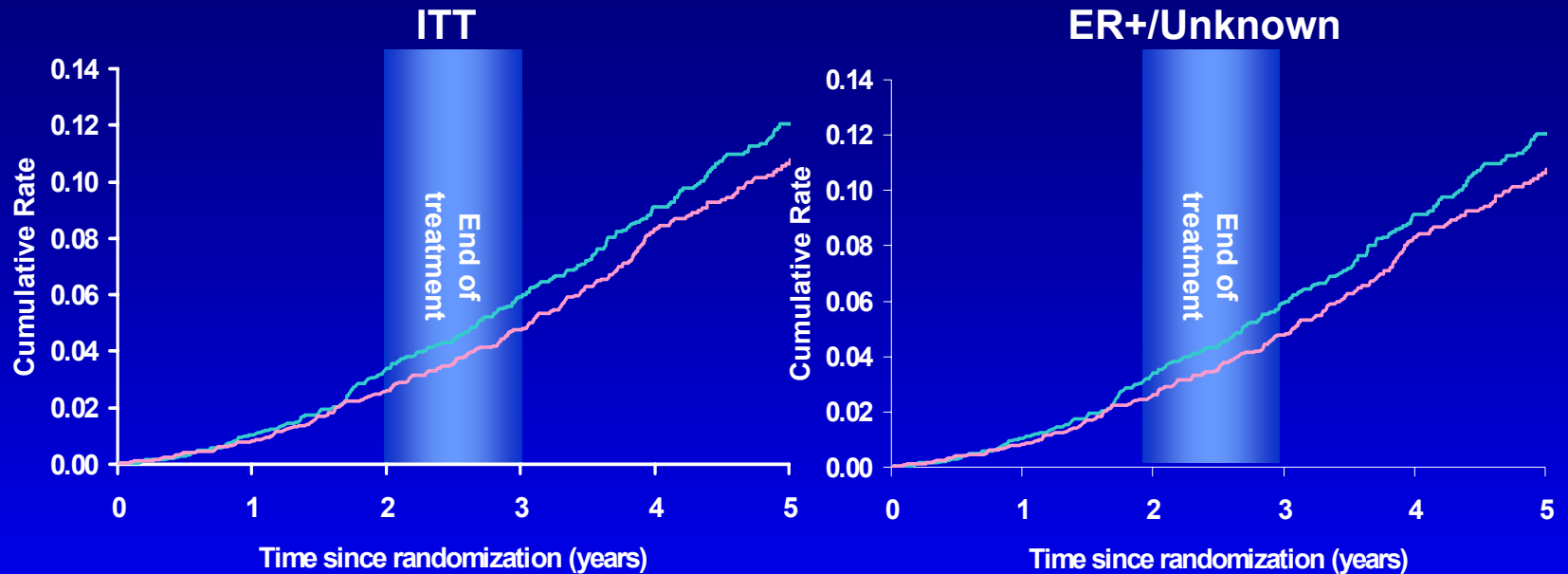
	Exemestane	Tamoxifen	Total
Total deaths	222	261	483
Breast cancer deaths	149	166	315
Intercurrent deaths	73	95	168
<i>COD known</i>	<i>65</i>	<i>80</i>	<i>145</i>
Other cancer	20	35	55
Vascular	17	11	28
Cardiac	14	13	27
Other	14	21	35
<i>COD unknown</i>	<i>8</i>	<i>15</i>	<i>23</i>

Overall Survival



year	2.5	5	2.5	5
% abs. diff. (95% CI)	0.8 (-0.4 – 1.9)	1.2 (-1.5 – 3.9)	0.7 (-0.4 – 1.9)	1.6 (-1.2 – 4.3)

Cumulative Hazard Rate - OS



— Exemestane — Tamoxifen

Annual Hazard Rate, % (95% CI)

ITT	1	2	3	4	5
Exemestane	0.8 (0.5, 1.2)	1.8 (1.3, 2.5)	2.2 (1.6, 2.9)	3.6 (2.8, 4.5)	2.3 (1.6, 3.4)
Tamoxifen	1.0 (0.7, 1.5)	2.4 (1.8, 3.1)	2.5 (2.0, 3.3)	3.2 (2.5, 4.1)	2.9 (2.1, 4.1)

Overall Survival – Subgroups

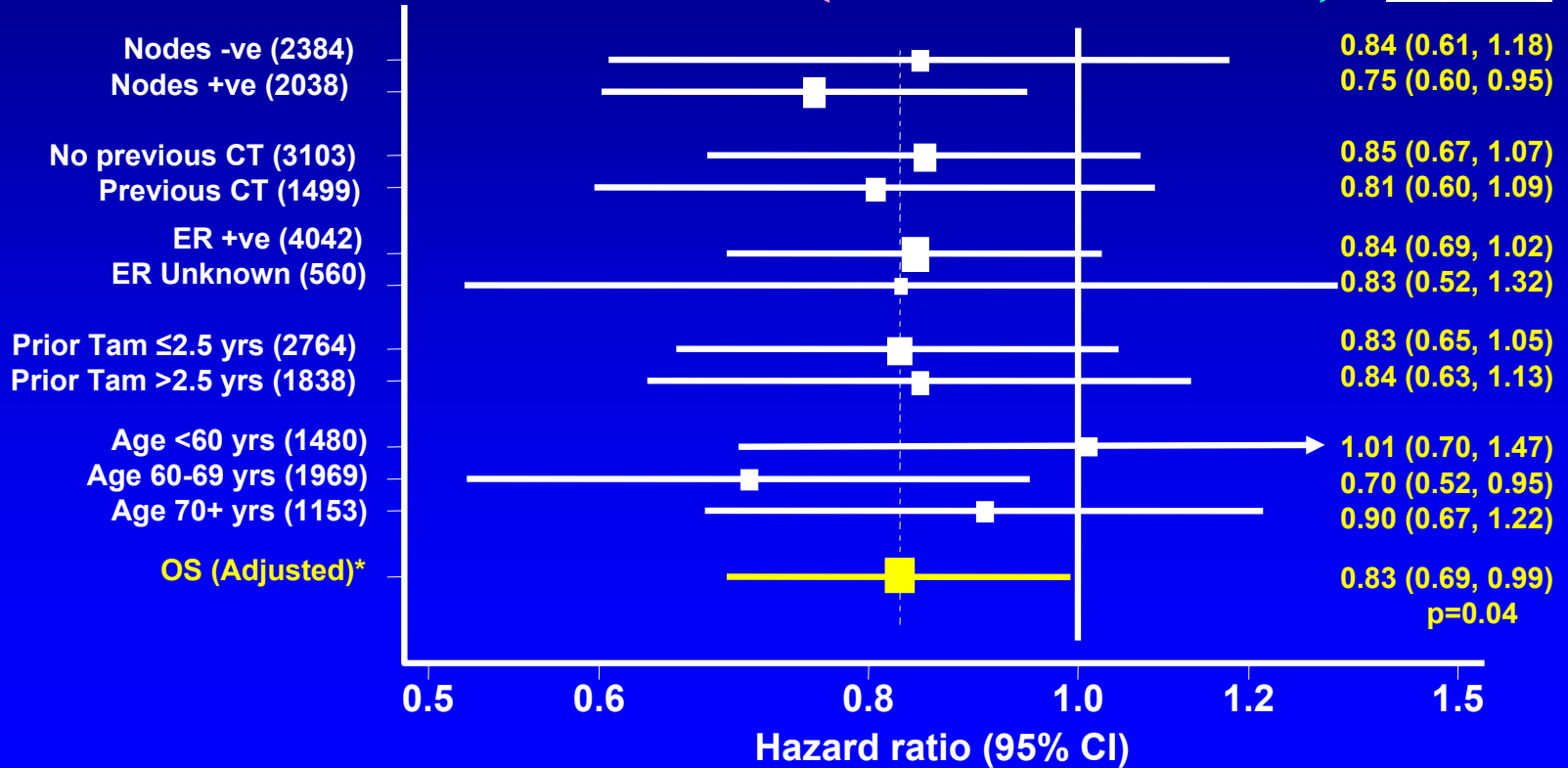
ER+/Unknown

Favors Exemestane

Favors Tamoxifen



HR (95% CI)



* Adjusted for Nodal Status, Chemotherapy Use & HRT Use

Sites of Other Invasive Cancers ITT

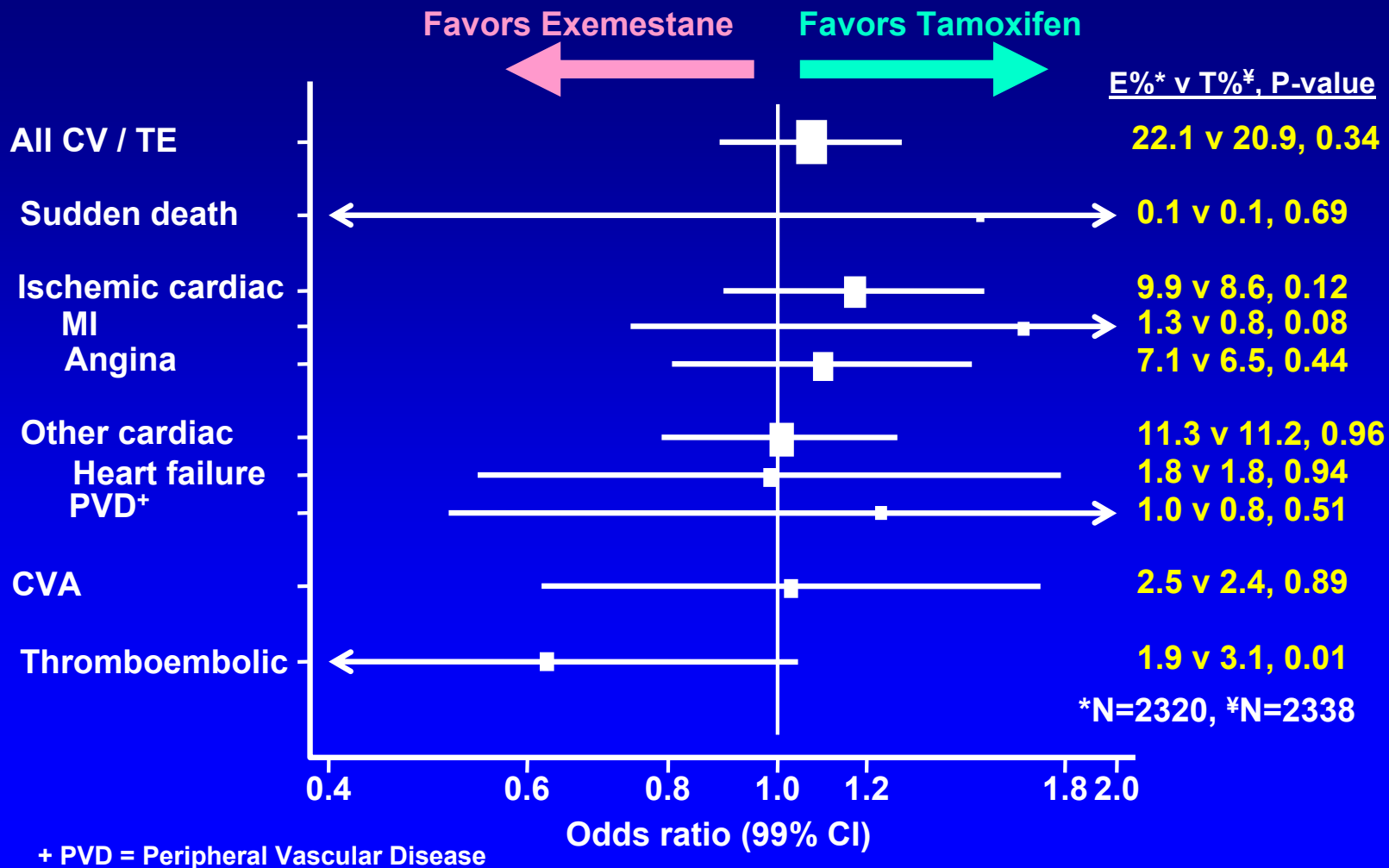
	Exemestane	Tamoxifen
Uterus	9	17
GI	18	28
Lung	9	15
Melanoma	4	5
Ovary	6	4
Other	26	38
Total Non-Breast 2nd Primaries	72	107

Safety Analysis

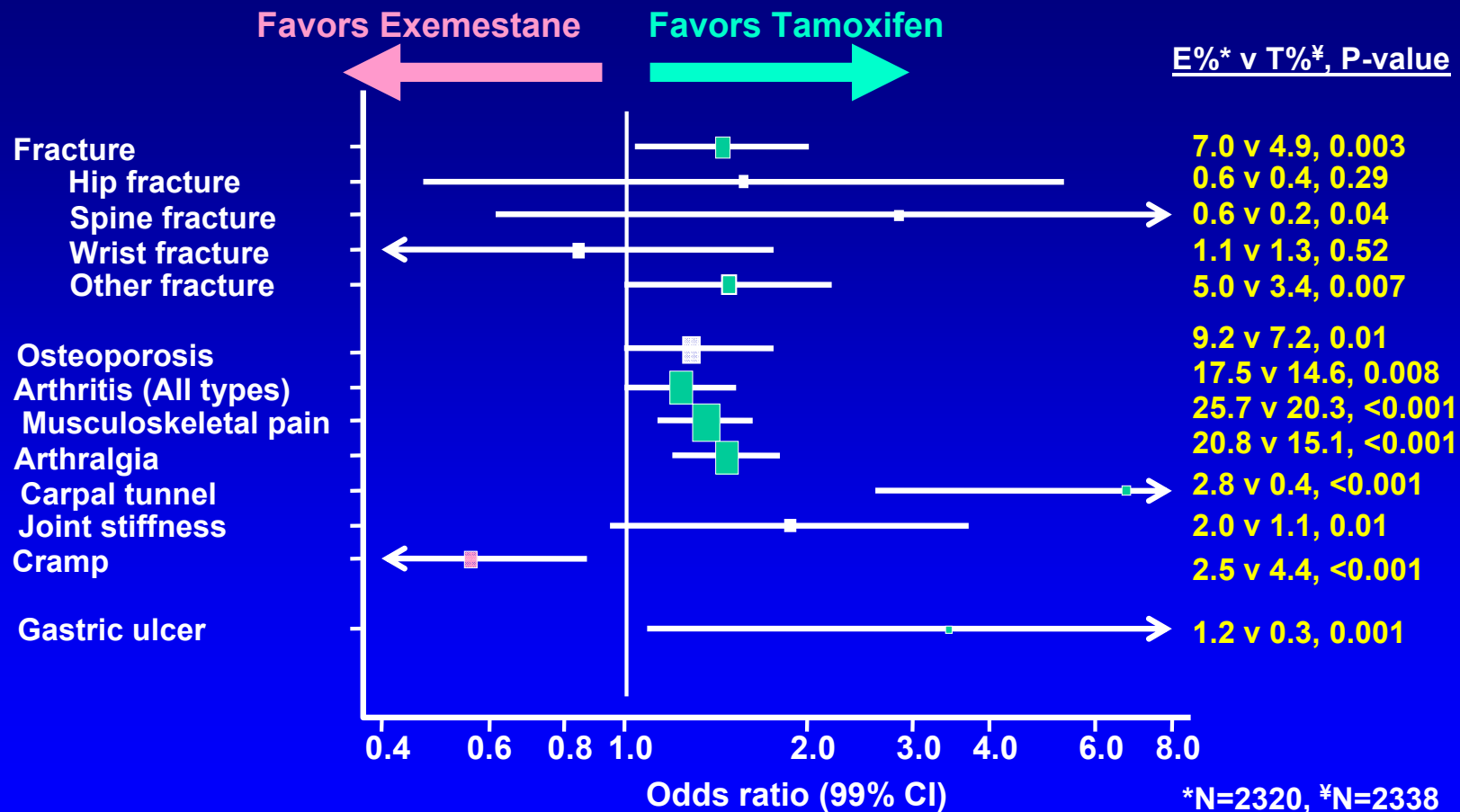
**As treated, on treatment and follow-up, censoring
at relapse**

Significant p-value < 0.01 – multiple testing

Cardiovascular / Thromboembolic



Musculoskeletal / Other

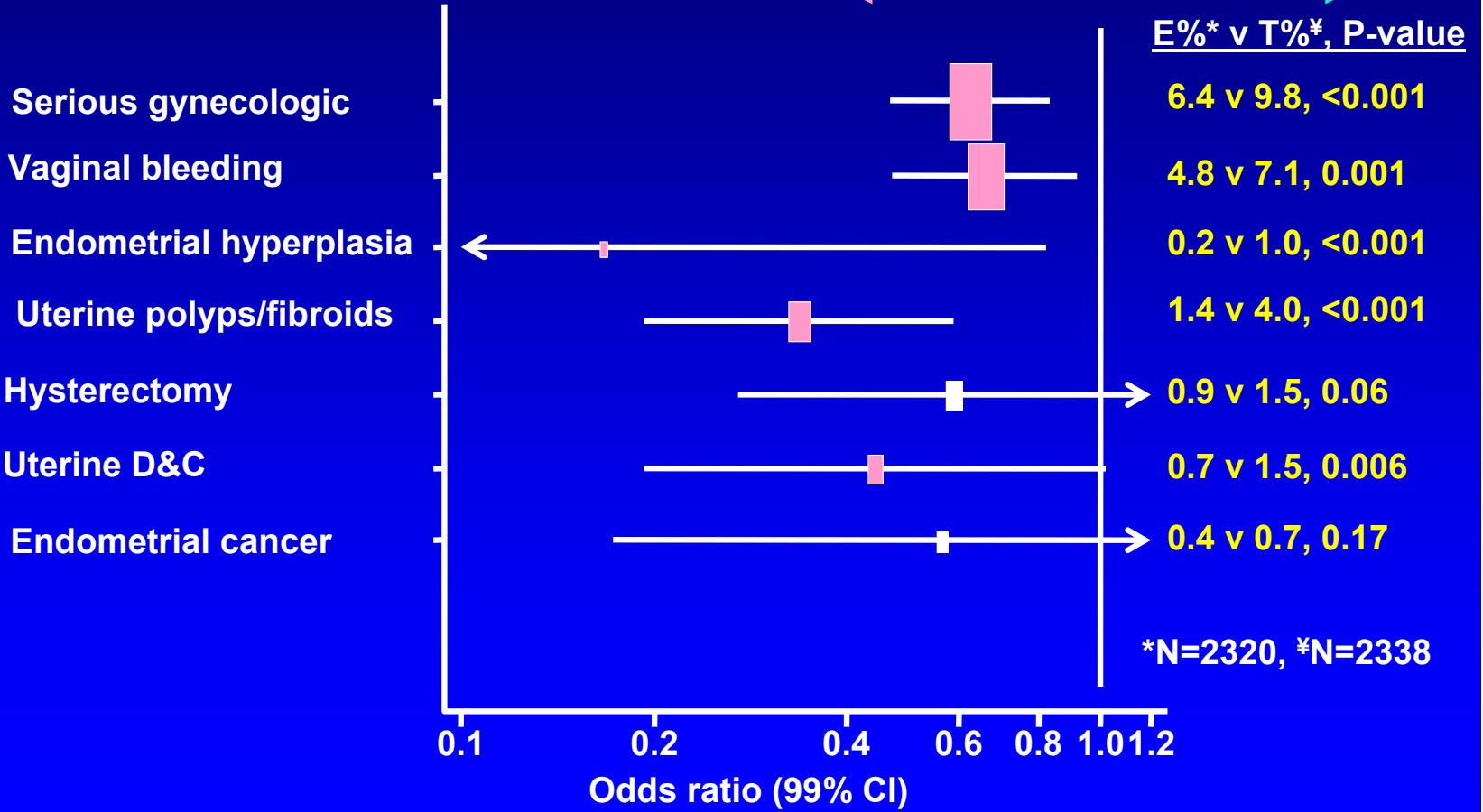


Incidence rate per 1000 women years (99% CI) for fractures (allowing more than one fracture event per patient) are E = 19.2 (15.9, 23.1) & T = 15.1 (12.2, 18.7)

Gynecologic

Favors Exemestane

Favors Tamoxifen



Conclusions

- Switching to Exemestane after 2-3 years of Tamoxifen reduces the risk of dying

ITT **15% (-2% - 29%) p=0.08**

ER+/Unknown **17% (0% - 31%) p=0.05**

p=0.04 (adjusted)

- Serious side effects are rare
- Switching strategy appears to minimize the adverse risks of both agents
- With 2-3 years post treatment follow-up, early disease related benefits appear to be maintained and Exemestane is safe and well tolerated

Acknowledgements



Imperial College
London



**The patients, doctors, nurses, data managers and monitors of
the 20 collaborative groups.**

The Steering Committee.

The Data Monitoring & Safety Committee.

**The staff at Imperial College and The Institute of Cancer
Research, London.**

CANCER RESEARCH UK 



Pfizer Oncology