

Expert PracticeSM in Breast Cancer

17th of April 2010, Athens - Greece

**Unanswered Questions
in Endocrine Therapy of Breast
Cancer in 2010**

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Adjuvant Hormonal Therapy Trial Designs

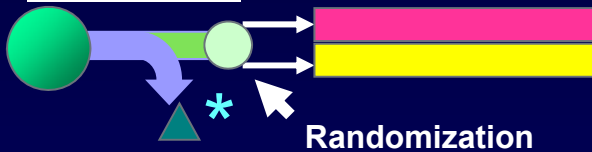
UPFRONT



SUPPORTING TRIALS

- ATAC
- BIG 1-98 straight arm
- TEAM

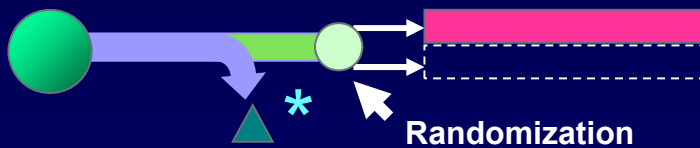
SWITCHING



SUPPORTING TRIALS

- IES
- ITA
- ARNO/ABCSG combined analysis

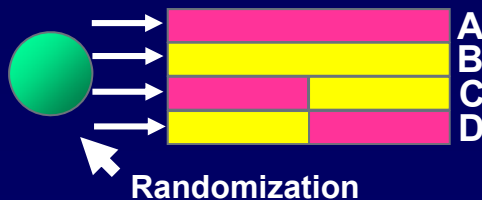
EXTENDED ADJUVANT



SUPPORTING TRIALS

- MA-17
- ABCSG 6a
- NSABP 33

SEQUENCING



SUPPORTING TRIALS

- ABCSG 8 alone (A&C)
- BIG 1-98 sequencing arms (C&D)
- TEAM

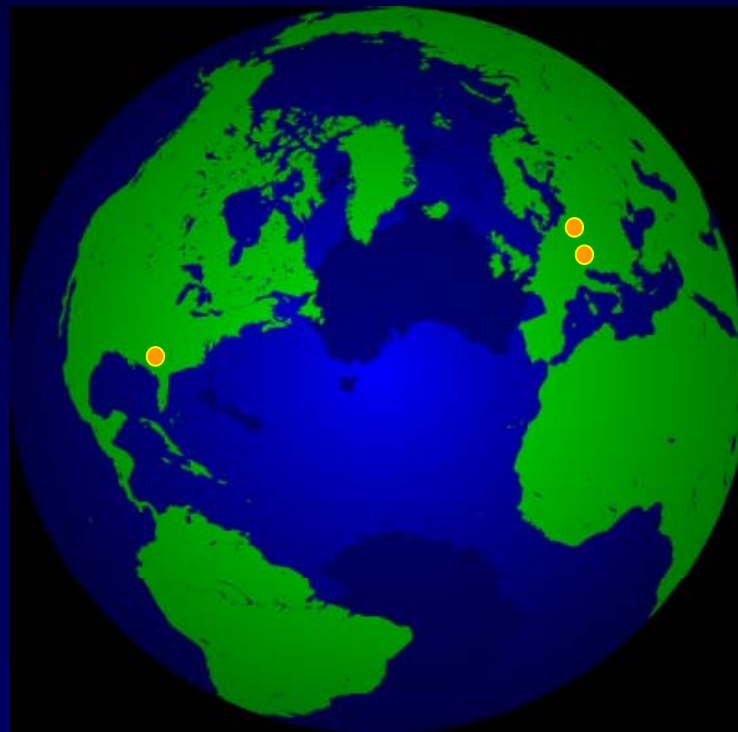
* Note that some patients from the original newly diagnosed population are lost due to recurrence or adverse events prior to randomization.

SABCS 2008

- AI meta-analysis
- BIG 1-98
- TEAM
- ABCSG 8

SABCS 2009

- BIG 1-98
- TEAM
- MA17



ECCO/ESMO Berlin 2009

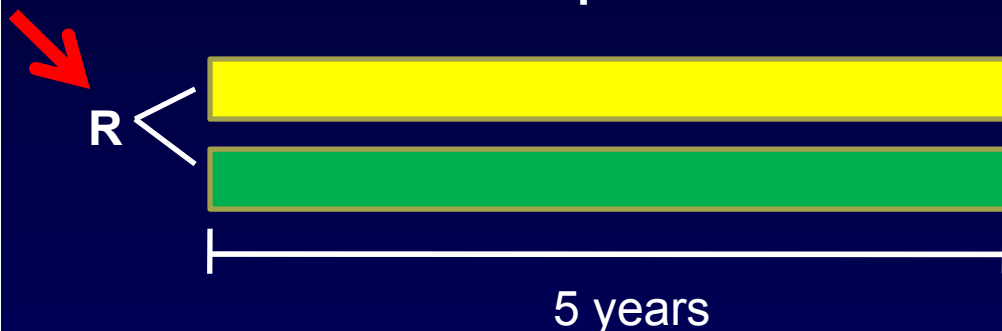
- IES

St Gallen 2009

- Consensus

Aromatase Inhibitors vs Tamoxifen as Adjuvant Therapy for Postmenopausal Women with Estrogen Receptor-Positive Breast Cancer: Meta-Analyses of Randomized Trials of Monotherapy and Switching Strategies

Cohort 1: Direct comparison as monotherapy

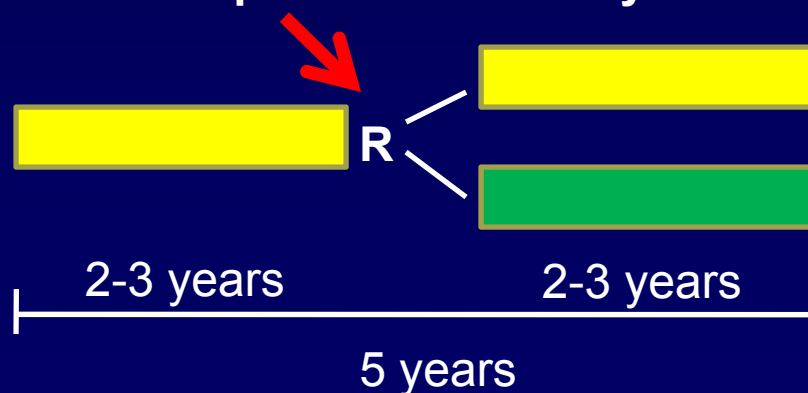


Trials

ATAC

BIG 1-98/BCSG 18-98

Cohort 2: Comparison after 2-3 years of tamoxifen



Trials

GABG/ARNO

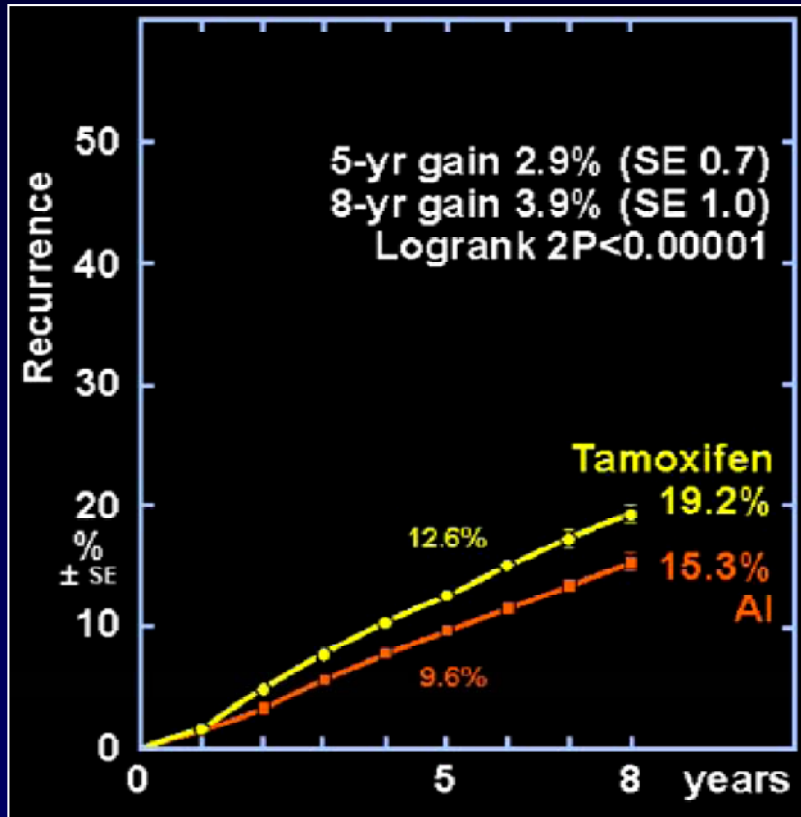
IES/BIG 2-97

ITA

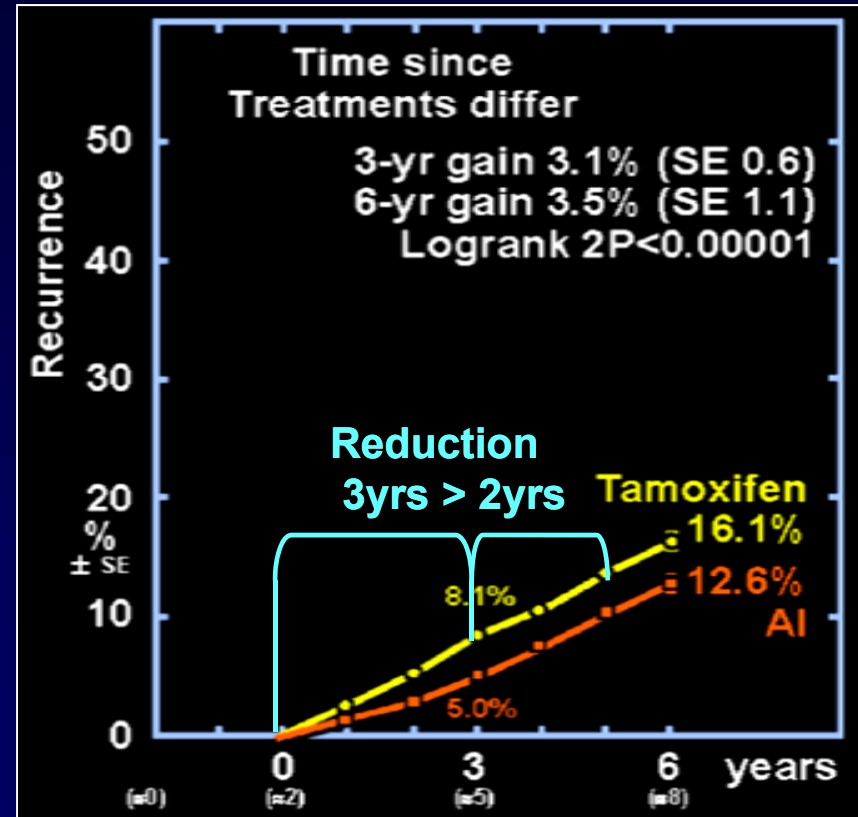
ABCSG VIII

Meta-Analysis: Recurrence

Cohort 1: Monotherapy
23% proportional reduction



Cohort 2: Switching
29% proportional reduction

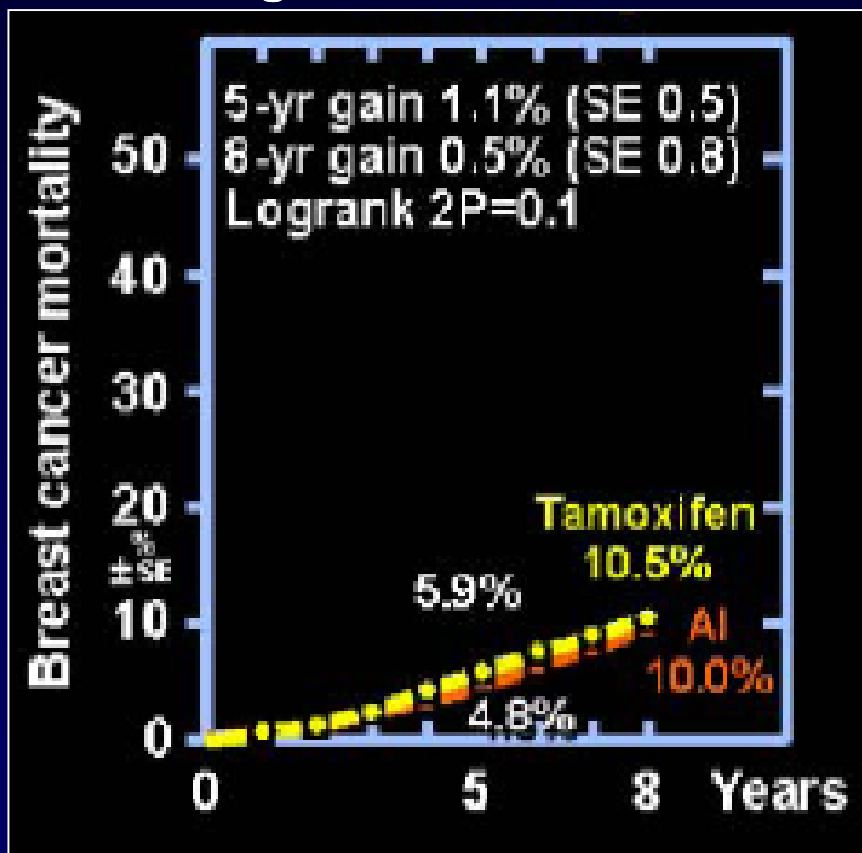


AI-treated patients had statistically significant improvements in recurrence-free survival in both cohorts

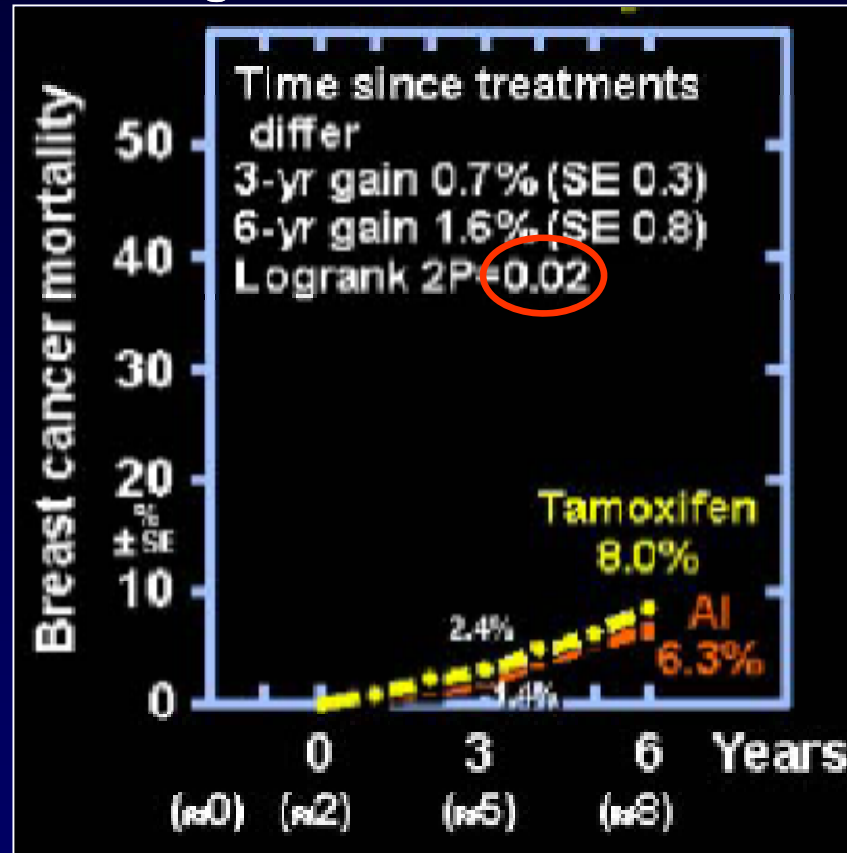
Note: These data cannot answer the question if “switching” is better

Meta-Analysis: Breast Cancer Mortality

Cohort 1: Monotherapy
No significant difference*



Cohort 2: Switching
Significant reduction



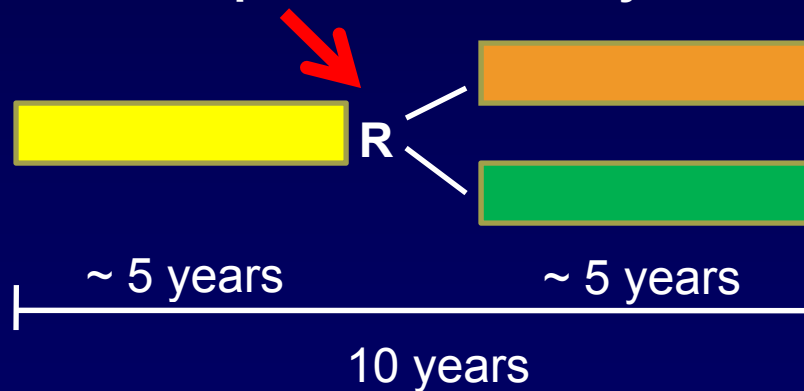
* Further follow-up may be needed, given experience with tamoxifen.

Note: These data cannot answer the question if “switching” is better

Aromatase Inhibitors (AIs) vs Not (Placebo/Observation) as Late Extended Adjuvant Therapy for Postmenopausal Women with Early-Stage Breast Cancer (BC): Overview of Randomized Trials of AIs After ~ 5 Years of Tamoxifen.

Goss P, Mamounas E, Jakesz R, Markopoulos C,
Dowsett M, Davies C, Godwin J, Peto R.
for the AIs Overview Group, SABCS Dec. 2009

Cohort 3: Comparison after ~ 5 years of tamoxifen



Trials

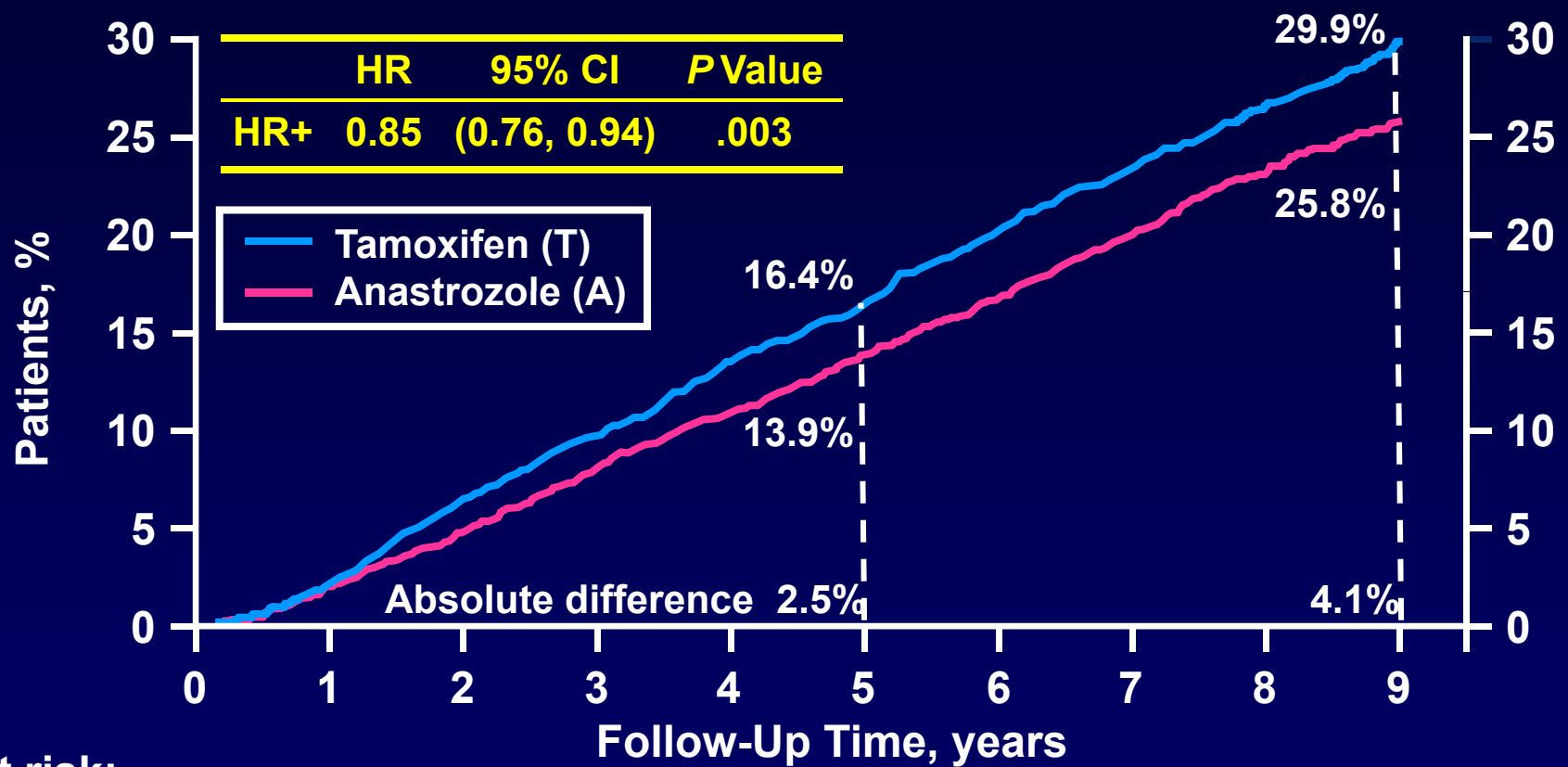
NCIC CTG MA17
NSABP B33
ABCSG 6a
ATENA

 Tamoxifen

 Placebo or Observation

 Aromatase inhibitor

ATAC: Disease-Free Survival HR+ Patients, 100-Month Median Follow-Up



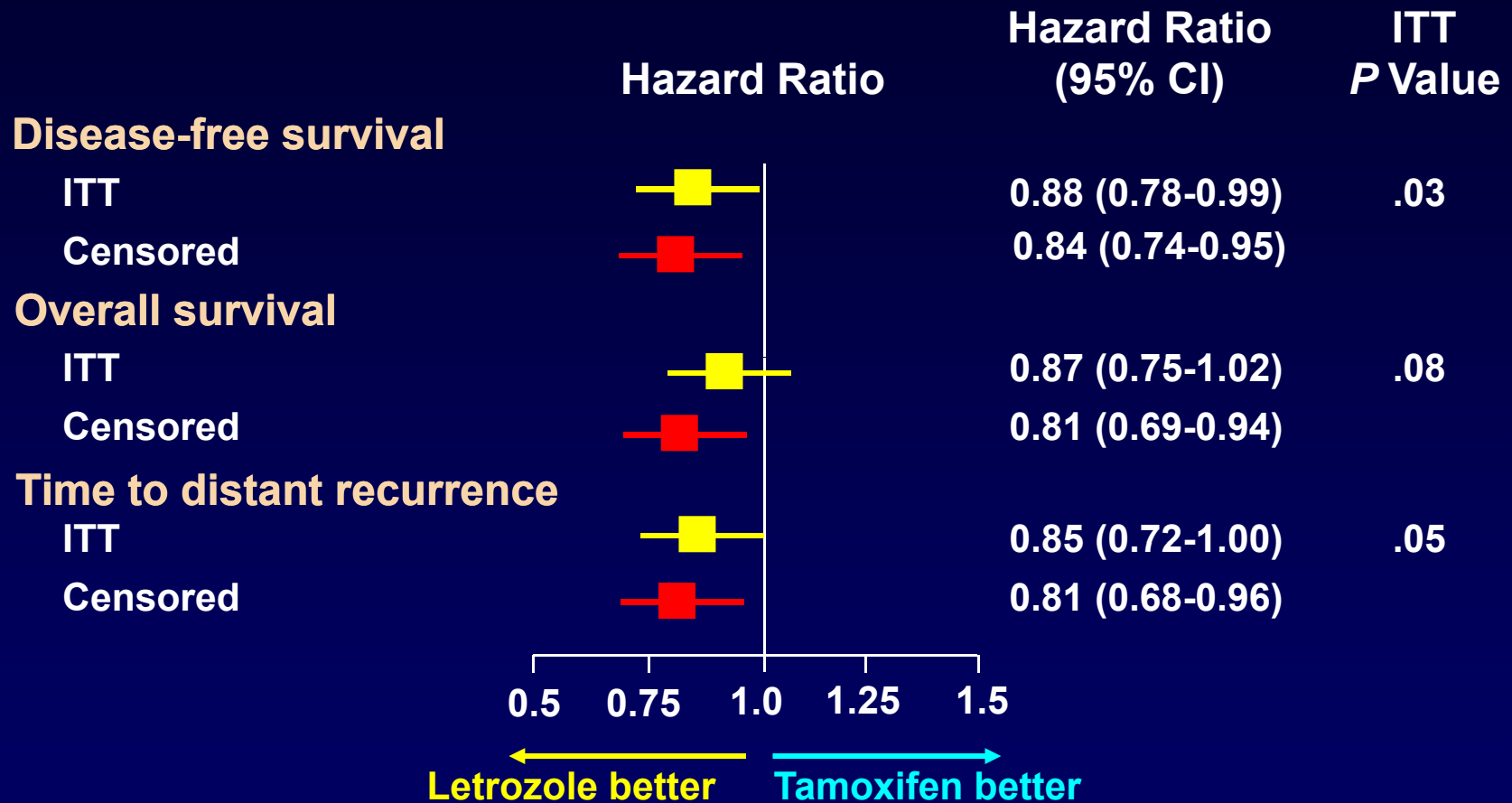
At risk:

A	2618	2541	2453	2361	2278	2159	1995	1801	1492	608
T	2598	2516	2400	2306	2196	2075	1896	1711	1396	547

Forbes JF, et al. *Breast Cancer Res Treat.* 2007;88(Suppl 1): Abstract 41. Forbes JF, et al. *Lancet Oncology.* 2008;9(1):45-53.

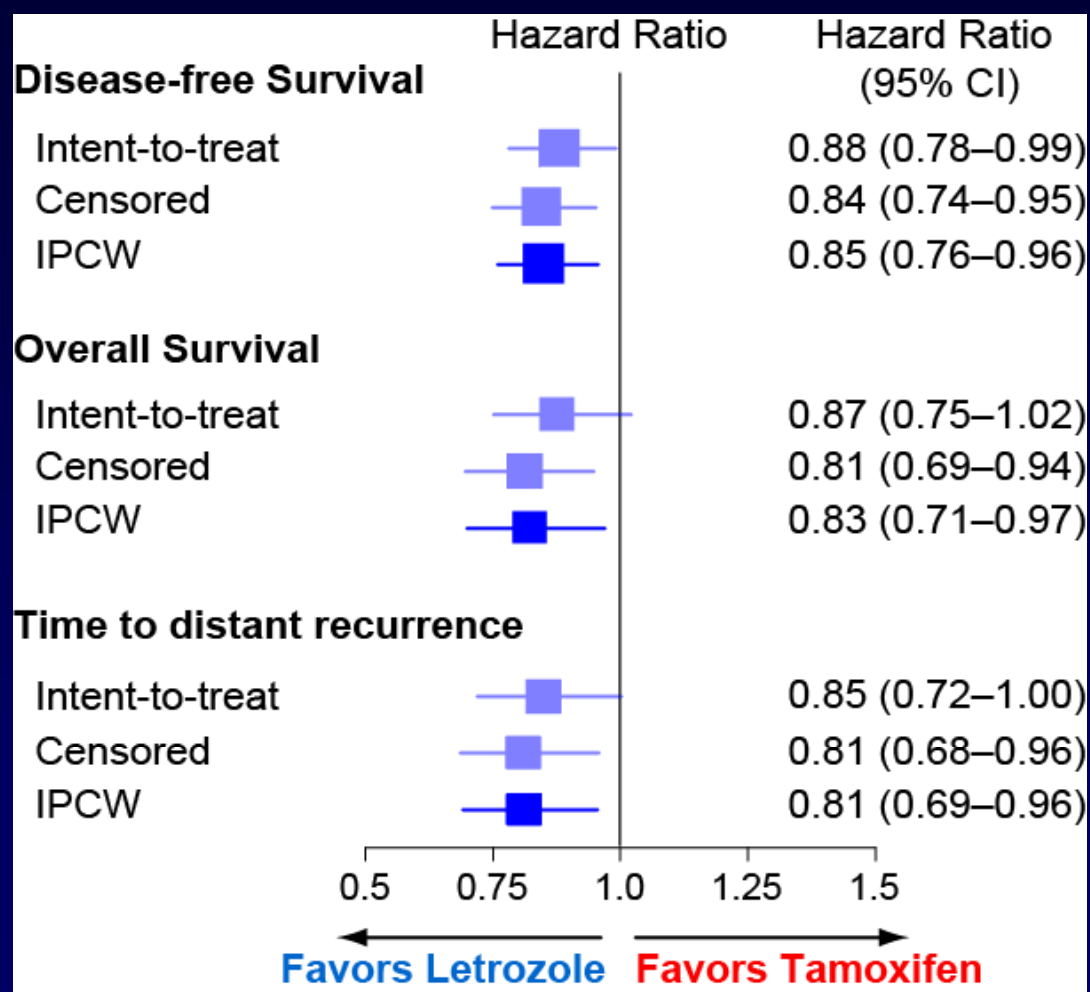
BIG 1-98 Monotherapy Update

Median Follow-Up 76 Months



Letrozole:Tamoxifen - Breast cancer events, 321:363
- Second (nonbreast) malignancy, 101:115
- Deaths without prior cancer event, 87:87

BIG 1-98 Monotherapy Update Including IPCW* Analyses



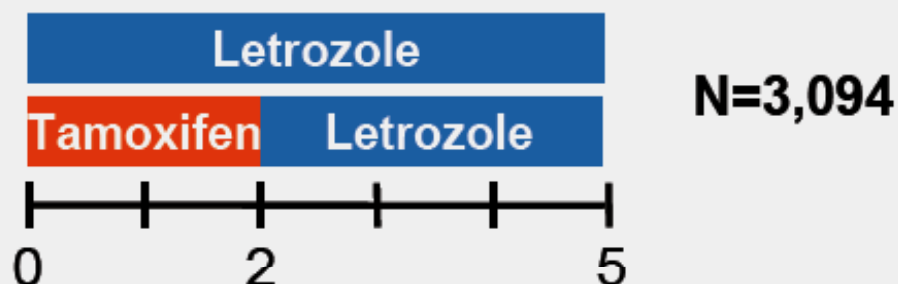
IPCW: Inverse Probability of Censoring Weighted Analysis

Regan MM, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 16.

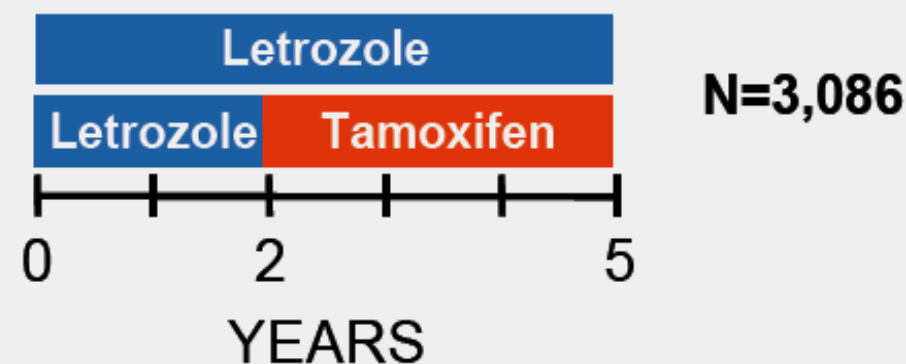
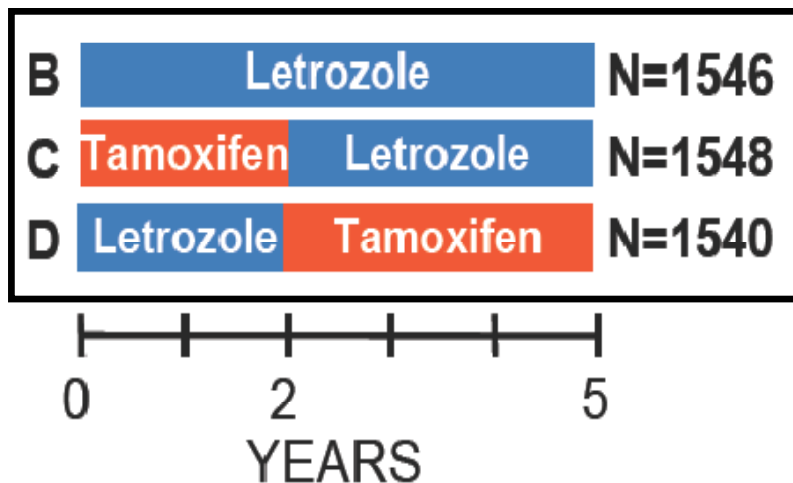
BIG 1-98 Sequential Therapy

Q.: Is a sequence of agents superior to letrozole monotherapy?

2-Arm Option



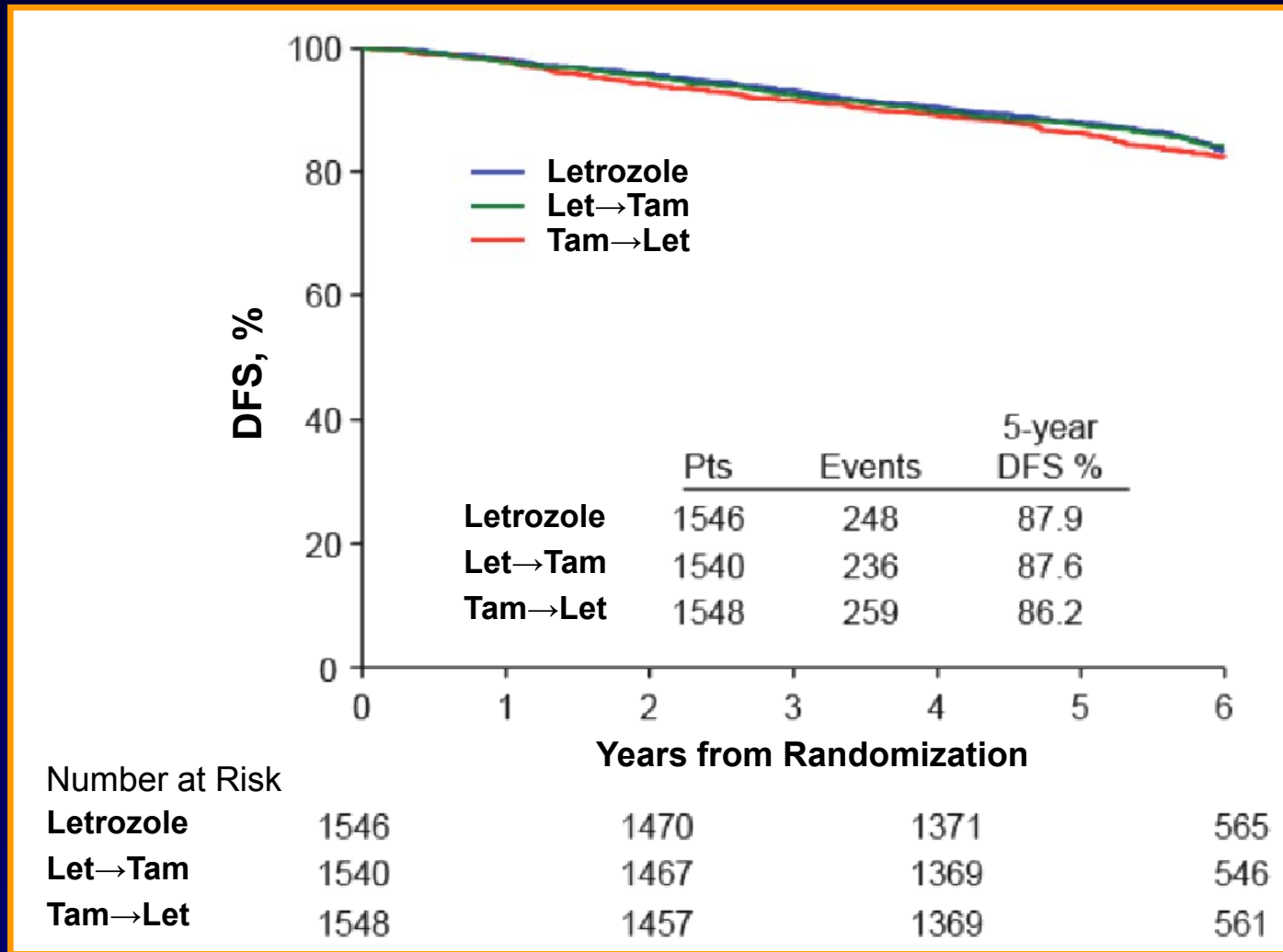
4-Arm Option



Evaluated from Randomization
(not switch)

Two Pairwise Comparisons

BIG 1-98 Sequential Therapy Disease-Free Survival



Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776.

Five Years of Exemestane as Initial Therapy Compared to Tamoxifen Followed by Exemestane for Five Years: The TEAM Trial, a Prospective, Randomized, Phase III Trial in Postmenopausal Women with Hormone-Sensitive Early Breast Cancer

N = 9775 accrued

Postmenopausal
receptor-positive
women

Diagnosis and
adequate
primary therapy
of early breast
cancer



R
A
N
D
O
M
I
Z
A
T
I
O
N

Tamoxifen

Exemestane

Exemestane

IES Positive Results

Total of 5 years' treatment

Co-primary
endpoints

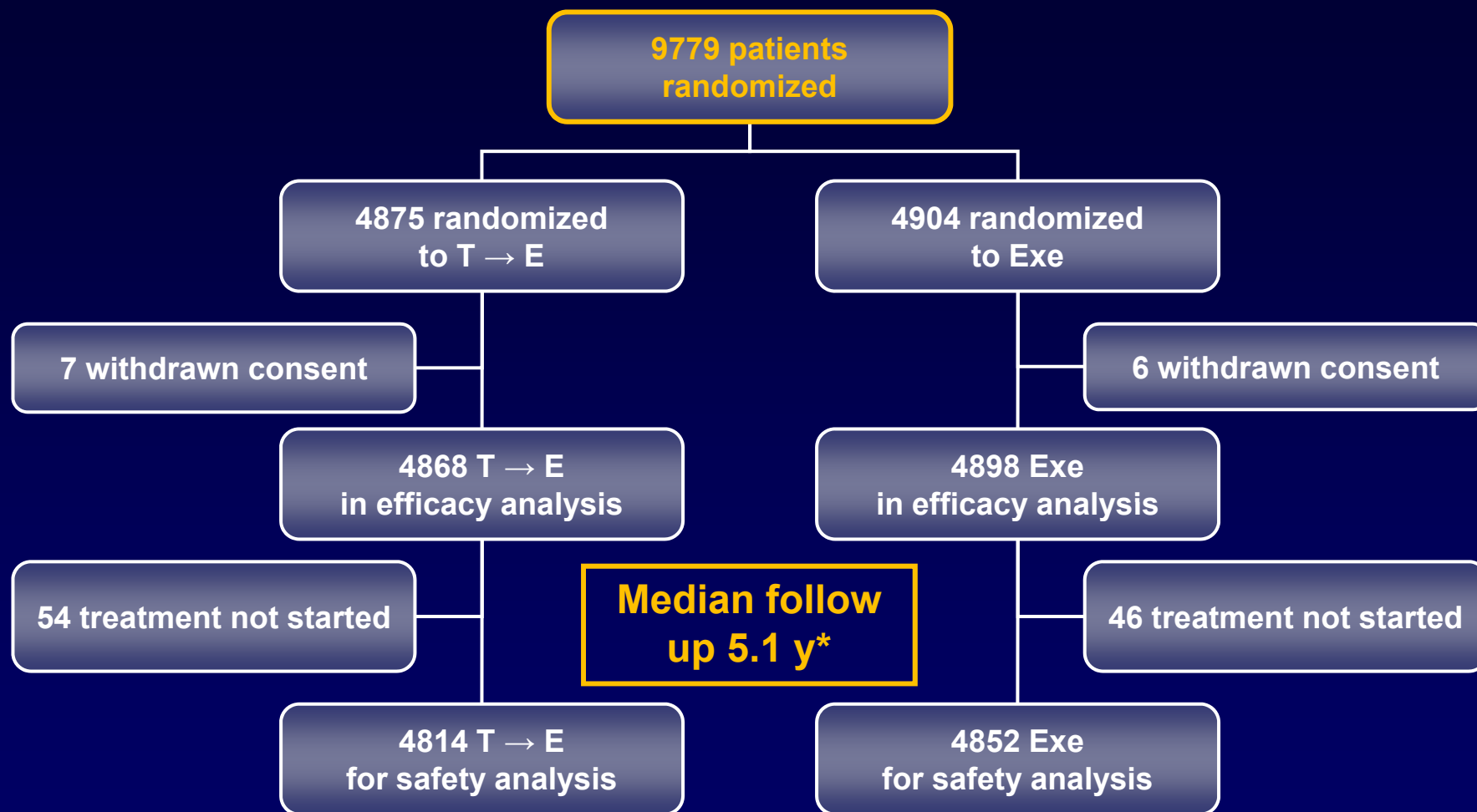
DFS at 2.75 years
DFS at 5 years

TEAM Trial: Revised Design 2004

Rea D, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 11.



Flowchart of TEAM Trial



* 60% of patients completed 5 years of follow up

Rea D, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 11.



DFS Events (ITT)

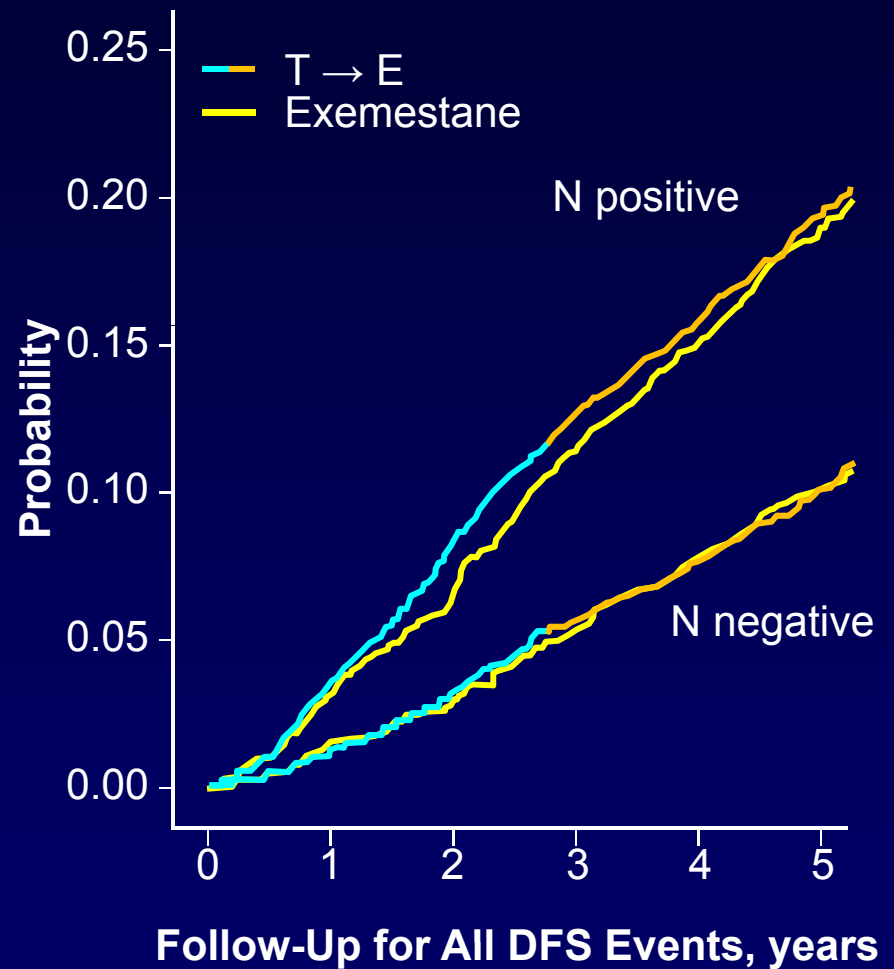
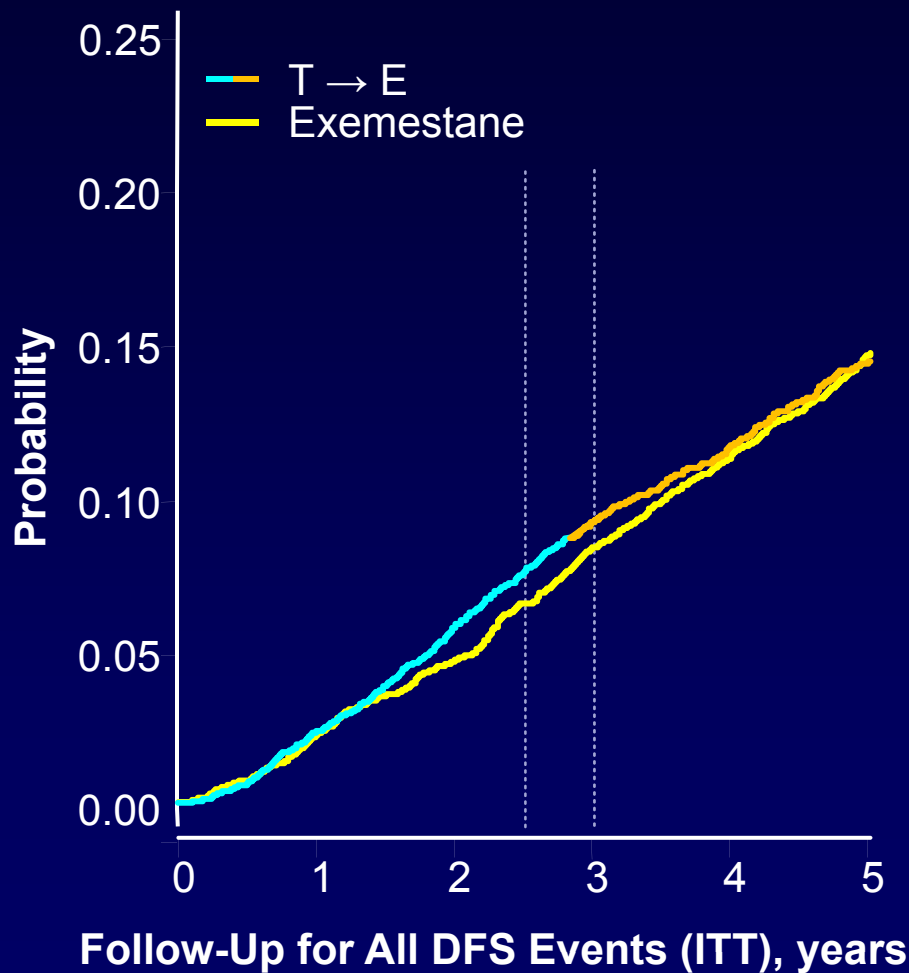
Event, n	T→E n = 4868	Exe n = 4898	Total n = 9766
Total DFS events	714	712	1426
Local recurrence only*	68	59	127
New primary BC	33	40	73
Distant metastasis	420	400	820
Intercurrent deaths	193	213	406

*incl. ipsilateral BC

Rea D, et al. *Cancer Res.* 2009;69(24 Suppl): Abstract 11.



Disease-Free Survival Events (Overall and According to Nodal Status)



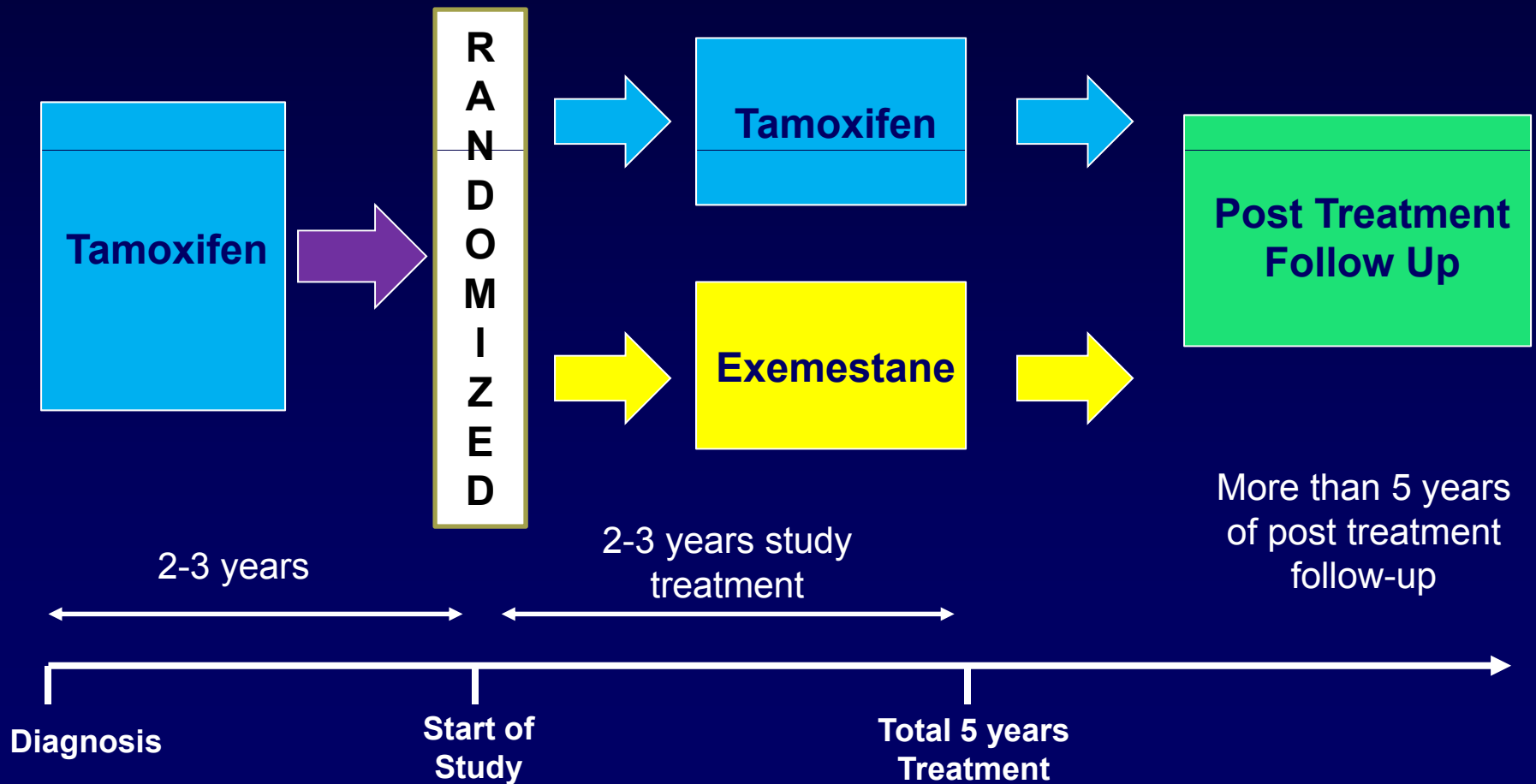


Conclusions

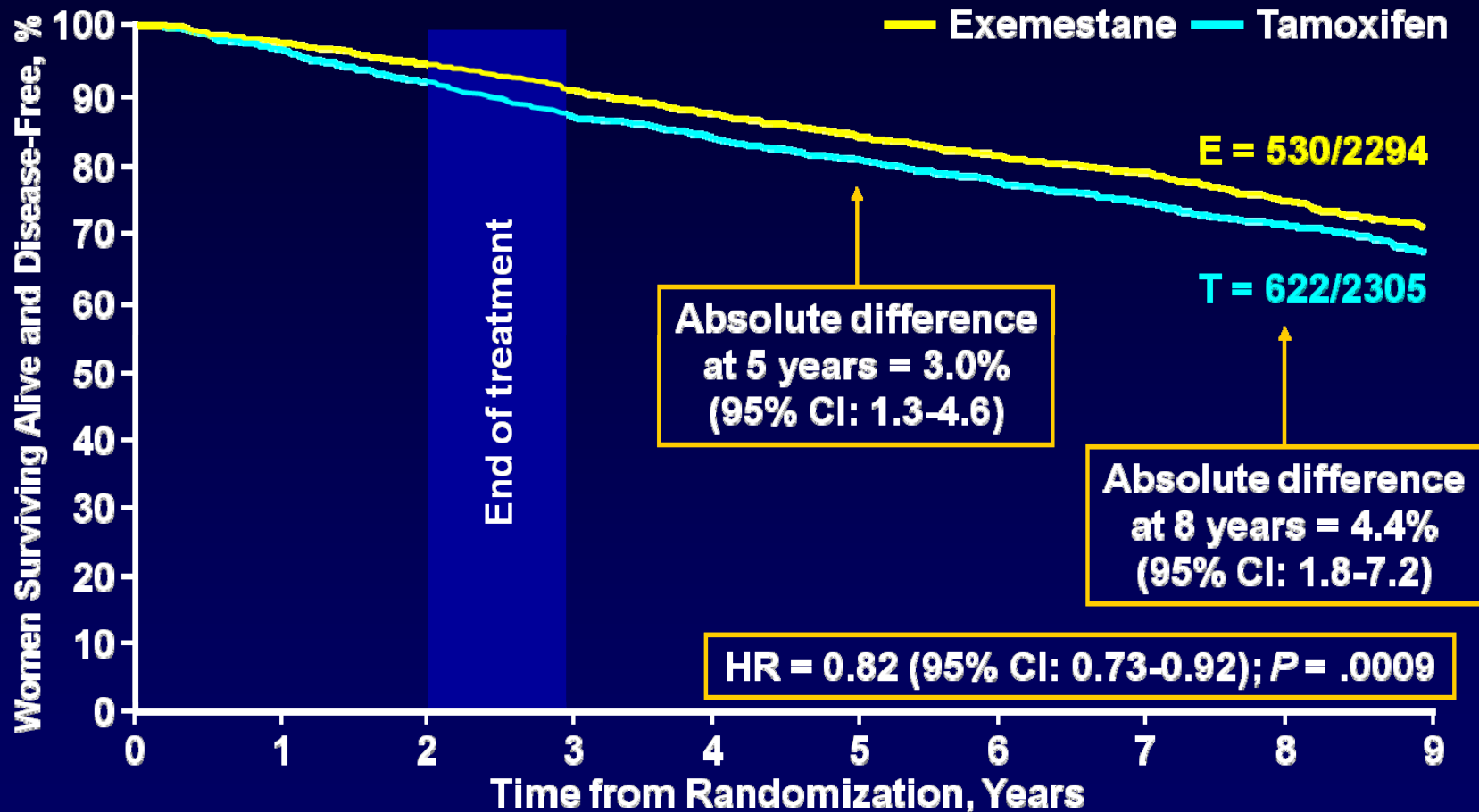
- TEAM did not show a difference in efficacy between 5-year upfront treatment with Exemestane compared to the sequence Tamoxifen → Exemestane
 - **Disease Free Survival (ITT):**
 - HR = 0.97 (95% CI 0.88 – 1.08); $P = 0.604$
 - **Time to Recurrence (ITT):**
 - HR = 0.94 (95% CI 0.83 – 1.06); $P = 0.293$
 - **Overall Survival (ITT):**
 - HR = 1.00 (95%CI 0.89 – 1.14); $P = 0.999$
- For postmenopausal patients with endocrine sensitive early breast cancer, the use of either 5 years of upfront Exe or T → Exe are appropriate treatment options.
- TEAM translational research may identify patient populations who could benefit more from one strategy over the other.

IES Trial Design

91 months median follow-up
Over 90% of patients had 6 years follow-up available
Over 99% of patient have completed treatment



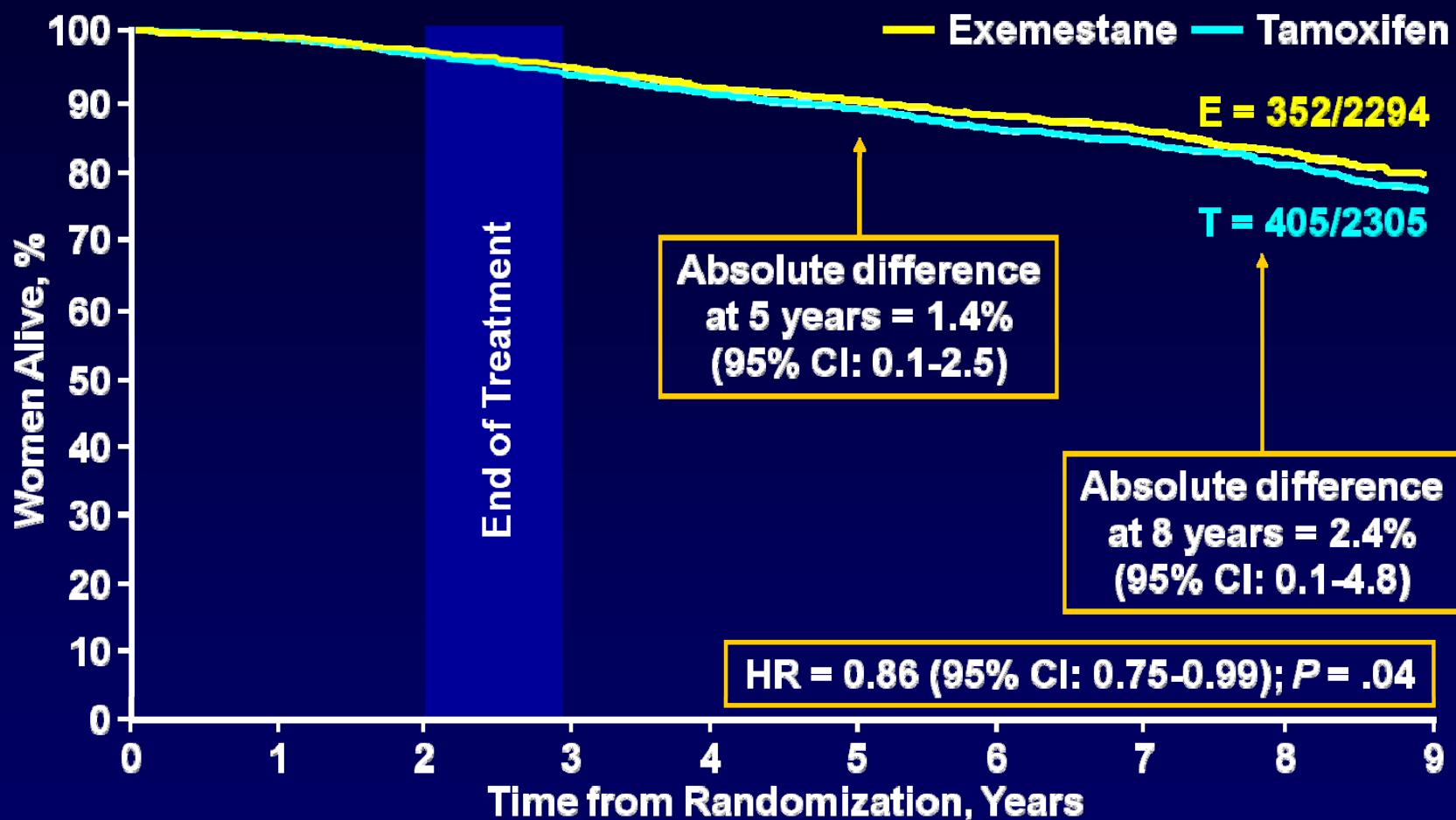
DFS: ER+/ER Unknown



Number of events/at risk

E	0/2294	55/2193	59/2124	80/2017	70/1915	67/1810	61/1662	51/1333	53/758	27+7*/267
T	0/2305	81/2193	101/2077	98/1948	69/1847	65/1745	70/1696	65/1244	44/676	22+7*/255

OS: ER+/ER Unknown



Number of events/at risk

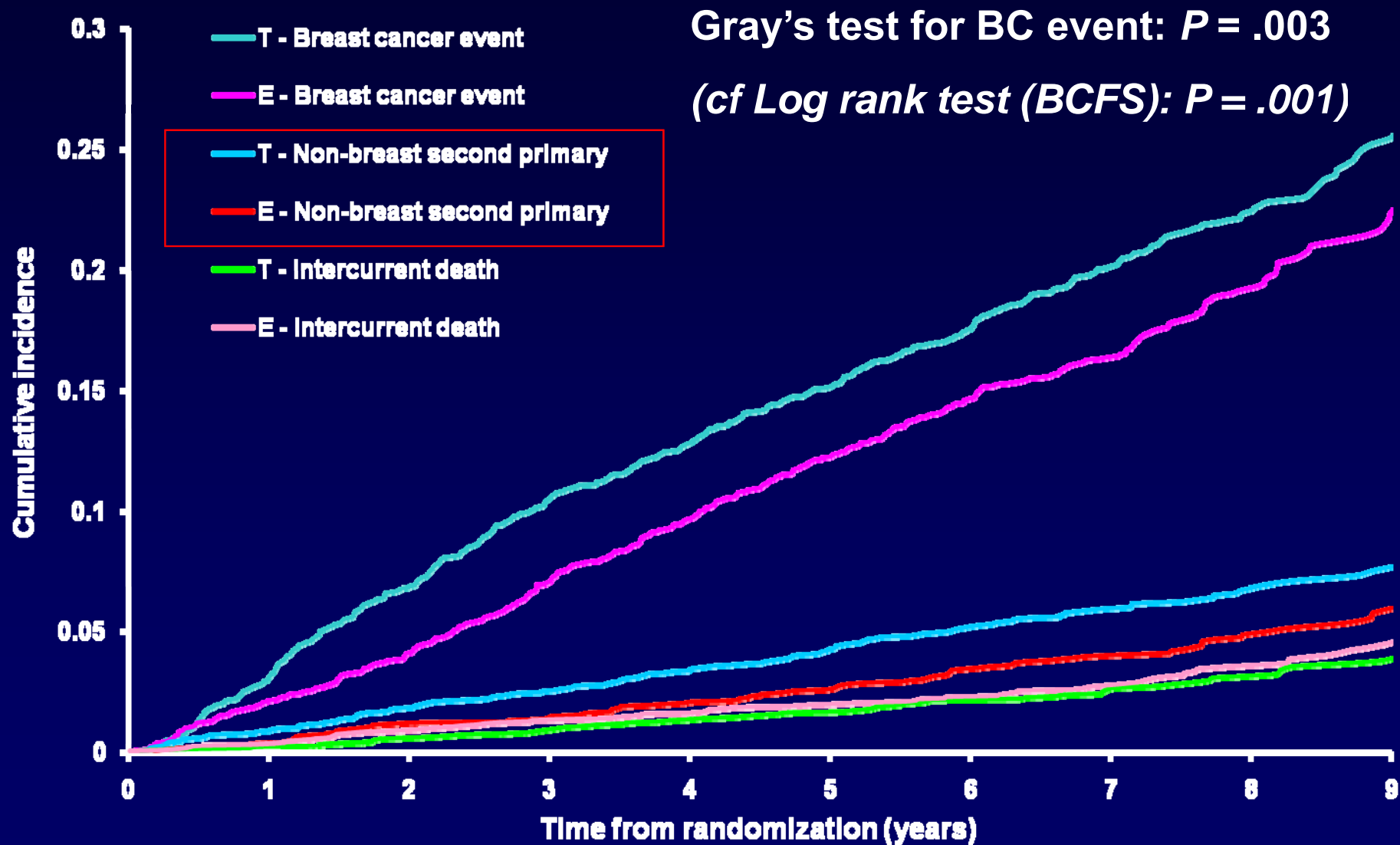
E	0/2294	17/2229	40/2177	42/2105	63/2006	36/1926	47/1781	42/1434	38/821	22+5*/291
T	0/2305	23/2249	52/2181	53/2094	63/1996	42/1912	61/1767	38/1411	14/767	23+6*/294

Sites of 1st Reported Distant Recurrence

	Exemestane	Tamoxifen	Total
	303	346	649
Visceral only	116	113	229
Bone only	75	109	184
Visceral + bone	52	55	107
Soft tissue/nodal only	25	23	48
Visceral + soft tissue/nodal	15	18	33
Visceral + bone + soft tissue/nodal	11	17	28
Bone + soft tissue/nodal	9	11	20

Events where site of recurrence is unknown are excluded

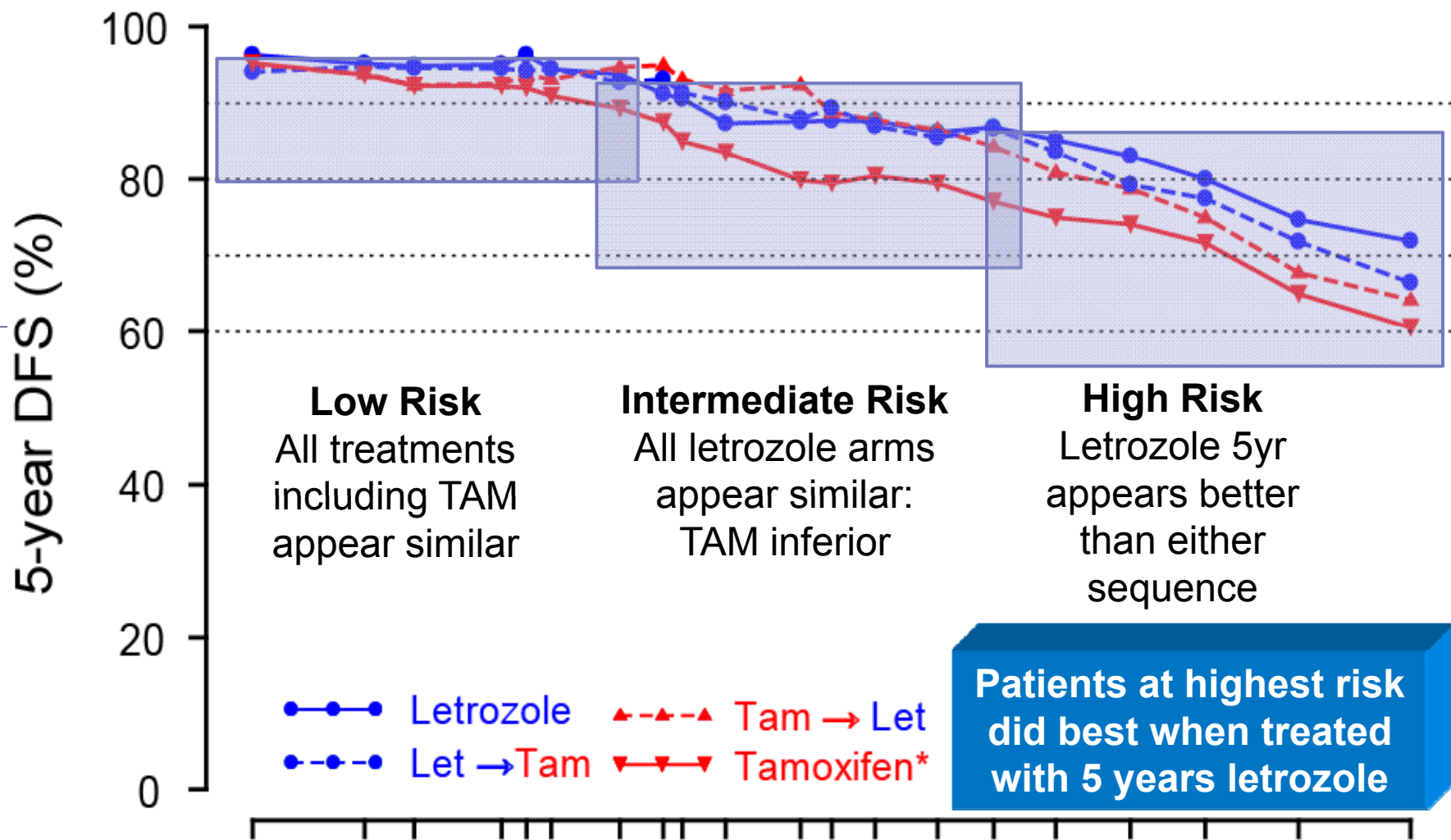
Competing Risks Analysis of Breast Cancer Outcome



IES Trial: Conclusions

- **In patients treated with tamoxifen 2-3 years, switching to exemestane as compared to continuing tamoxifen out to 5 years results in:**
 - **Persistent improvement in breast cancer outcomes out to 9 years**
 - **Findings from exploratory analyses requiring further validation**
 - Suggestion of smaller number of recurrences involving bone
 - Smaller number of—apparently real—non-breast 2nd primary cancers
 - **Modest but persistent improvement in overall survival**
 - ~50% fewer patients with distant recurrence—consistent with 2.4% improvement in overall survival

BIG 1-98: STEPP 5-Year DFS by Composite Risk



Low Risk
All treatments including TAM appear similar

Intermediate Risk
All letrozole arms appear similar: TAM inferior

High Risk
Letrozole 5yr appears better than either sequence

●—●—● Letrozole
 ▲-▲-▲ Tam → Let
●-●-● Let → Tam
 ▼-▼-▼ Tamoxifen*

Patients at highest risk did best when treated with 5 years letrozole

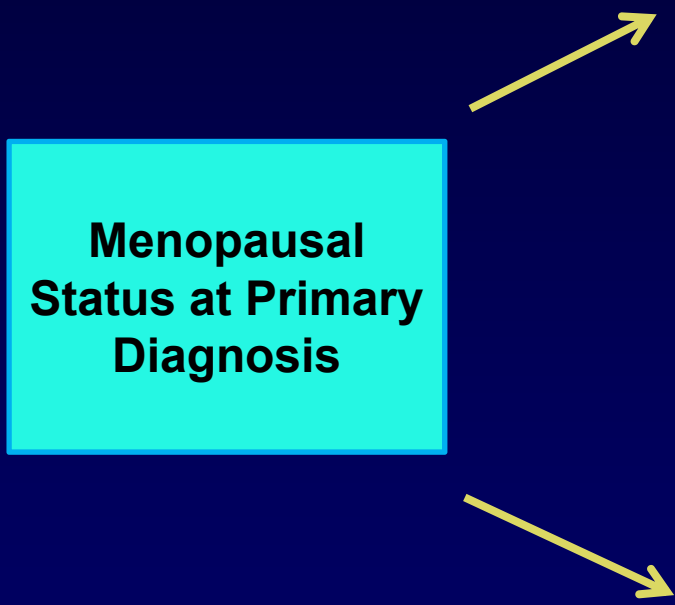
Increasing Composite Risk ➔



Extended Adjuvant Endocrine Therapy in Premenopausal Early-Stage Breast Cancer

An Analysis of Younger Women from MA.17

**Menopausal
Status at Primary
Diagnosis**



Premenopausal n = 889

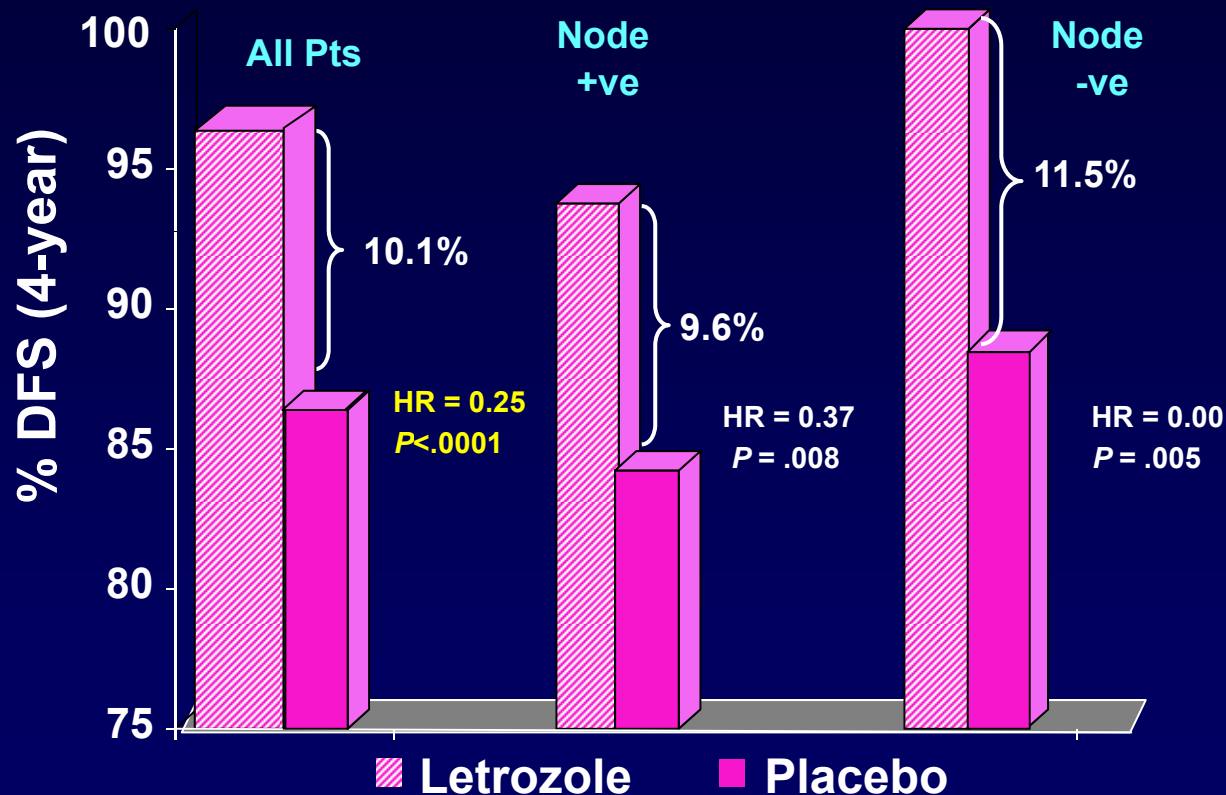
- <50 years of age with menses but underwent subsequent bilateral oophorectomy when tamoxifen started OR
- <50 years of age with menses when tamoxifen started but became amenorrhoeic during adjuvant chemotherapy or on tamoxifen

Postmenopausal n = 4277

- ≥50 years of age without menses at diagnosis OR
- <50 years of age without menses and considered postmenopausal at diagnosis OR
- Considered postmenopausal by virtue of menopausal LH/FSH

Conclusions

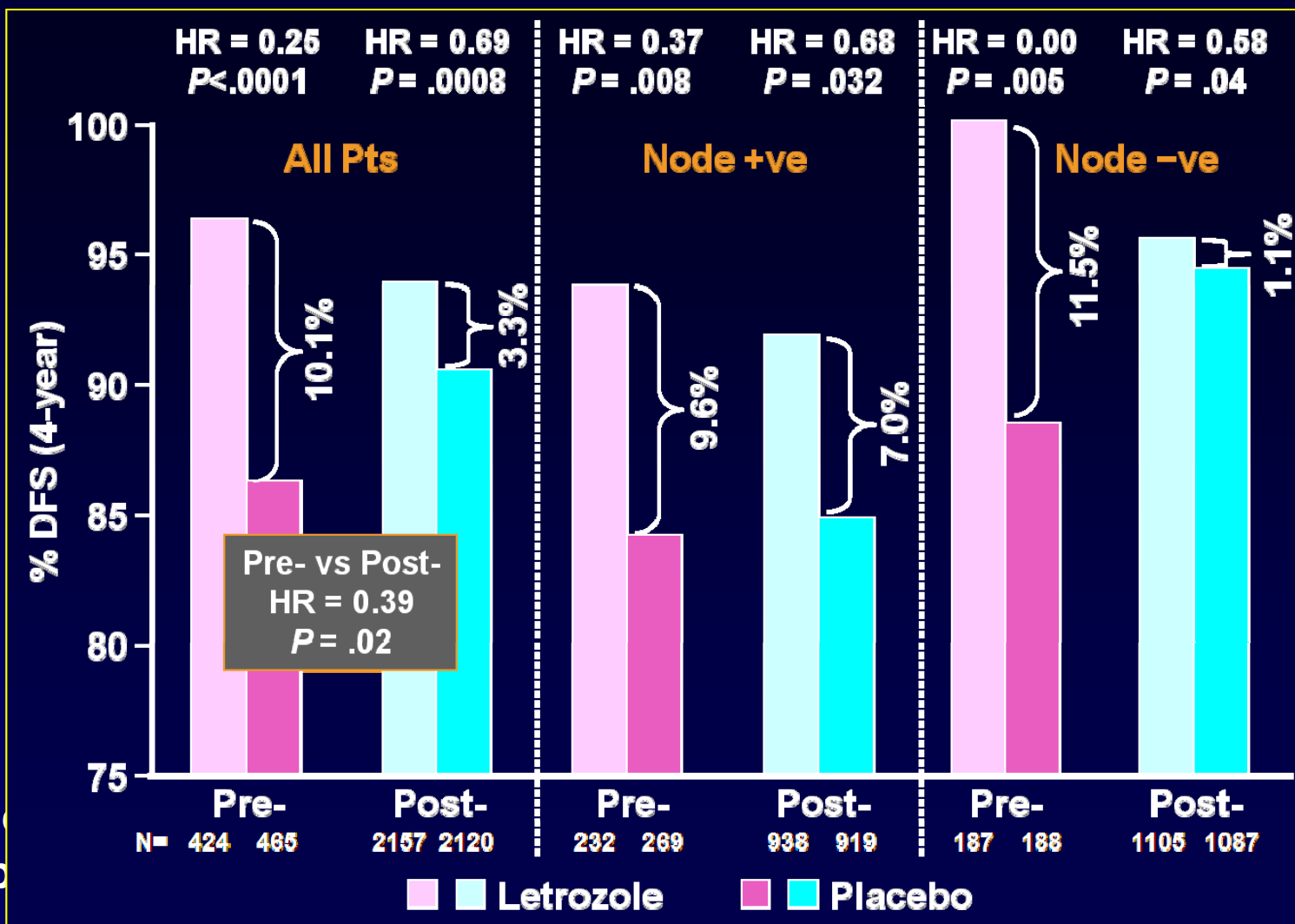
1. ER+ Premenopausal Breast Cancer Patients benefit significantly from Extended AI therapy after they become menopausal



2. The benefit was similar in women who delayed endocrine therapy up to 6 years after tamoxifen

Conclusions

- ER+ Premenopausal Breast Cancer Patients benefit significantly from Extended AI therapy after they become menopausal



2. The up

apy

Adjuvant Endocrine Therapy for Postmenopausal Breast Cancer

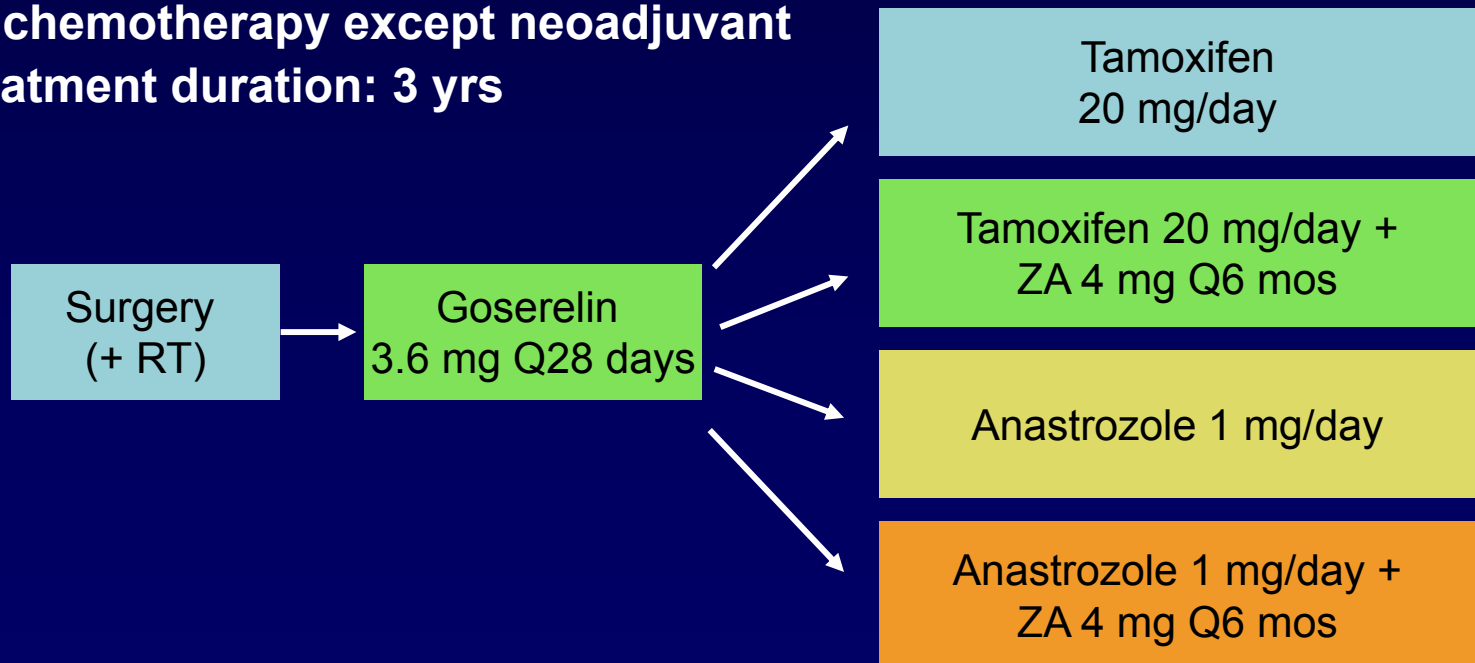
- **Highly endocrine-responsive** disease should require > 50% ER staining (73%)
- **AIs should be used** initially or after a period of Tam (68%)
- **Upfront AI** therapy is highly supported (69%) especially in LN positive patients
- **Tamoxifen alone** may still be a good option for some pN_0 patients with low recurrence scores (73%)
- **A molecular gene profile** should be used if uncertainty remains regarding prognosis/therapy after considering clinical and pathologic factors for endocrine-responsive patients (76%)
- **Proper duration** of AI treatment (5 years: 38% Yes, 23% No, 38%?)
- **CYP 2D6 testing** for patients receiving tamoxifen (26% Yes, 64% No)
- **Ki-67** as a predictive factor for AI treatment (30% Yes, 59% No)
- **IV zoledronic acid** 4 mg/6 months for patients on AI and *normal bone health* (26% yes, 59% No)

Unanswered Questions

- **Ovarian suppression and AI in premenopausal patients**
 - SOFT (*T vs OFS+T vs OFS+E*), TEXT (\pm Chemo, *OFS+T vs OFS+E*)
- **Best AI therapy**
 - FACE (*letrozole vs anastrozole*)
 - MA.27 (*exemestane vs anastrozole*)
- **Optimal duration of therapy with AIs**
 - MA.17R (*10 years vs 5 years*), NSABP B-42 (*T→AI switch \pm Letrozole*), SALSA-ABCSG 16 (*HT 5yrs + Ana 2yrs vs 5 yrs*)
 - Mode of administration of extended AI: SOLE (*treatment-free intervals*)
 - Role for tamoxifen following AIs
- **Genomics in the selection of appropriate hormone therapy**
 - Should any patients receive tamoxifen upfront?
 - Who is at the highest risk of late relapse?
 - What factors define resistance to hormone therapy?
- **Role of adjuvant bisphosphonates**
 - Update ABCSG 12 (ASCO 2010)

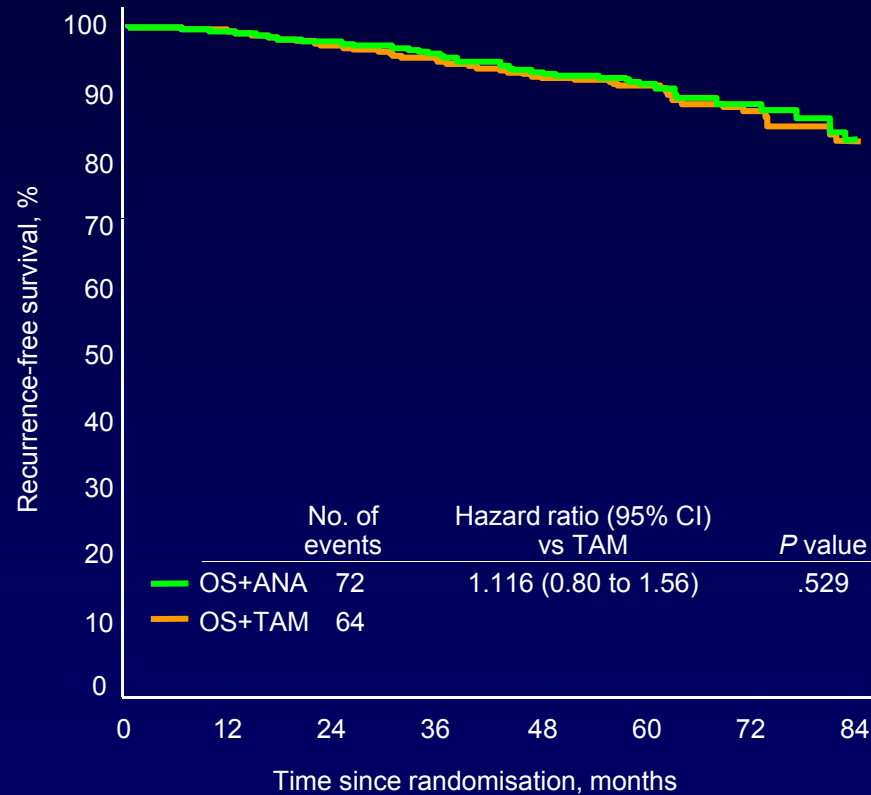
ABCSG-12 Trial Design

- Accrual 1999-2006
- 1803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PgR positive)
- Stage I and II, < 10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 yrs

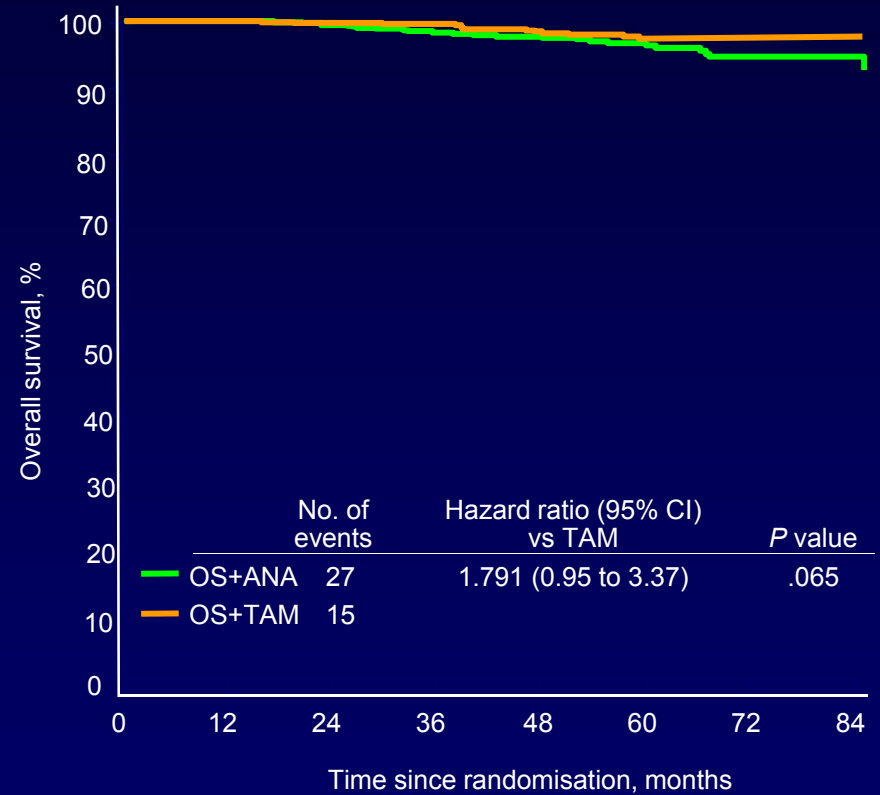


ABCESG 12: Effects of Endocrine Strategies on Disease Outcomes

Relapse-Free Survival



Overall Survival



Number at risk

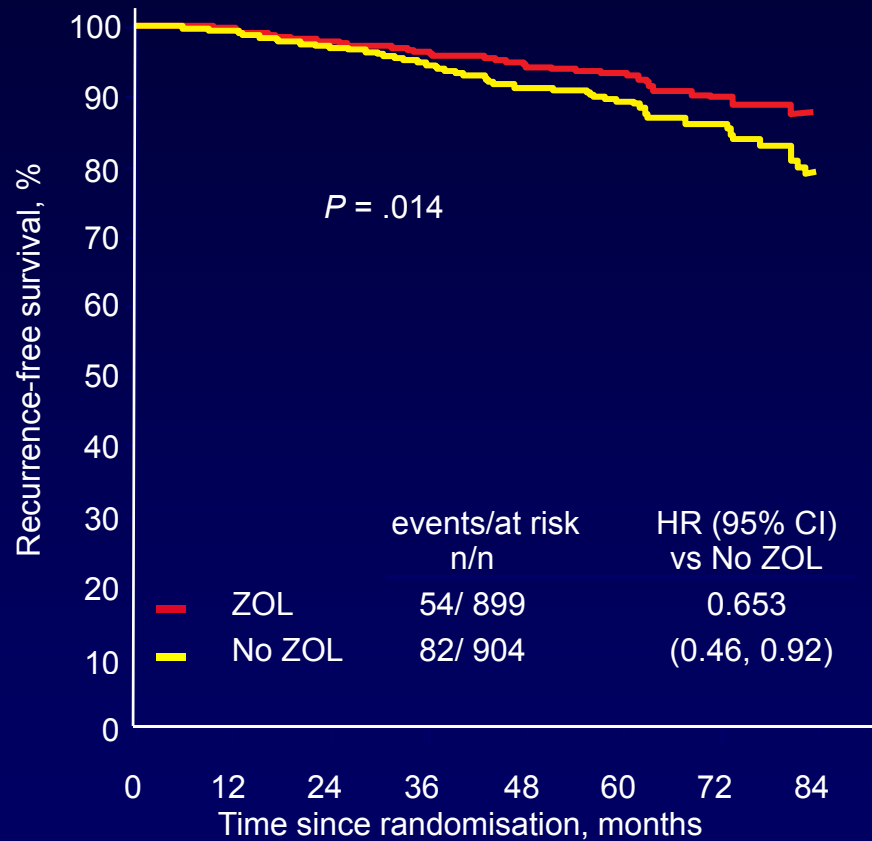
TAM	900	834	719	553	411	243	129	50
ANA	903	844	725	540	411	255	139	51

900	840	736	580	439	264	141	60
903	849	743	558	436	271	151	59

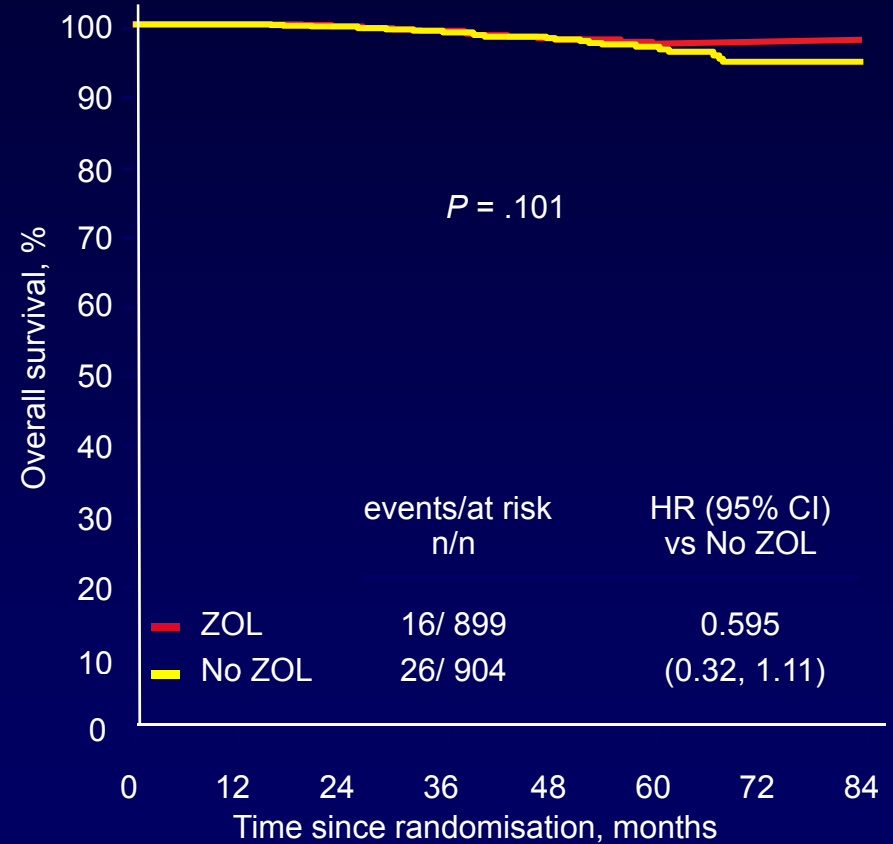
Gnant M, et al. *N Engl J Med.* 2009;360:679-691.

ABCESG-12: Effects of Zoledronic Acid on Disease Outcomes

Relapse-Free Survival



Overall Survival



Patients at risk

No ZOL	904	832	714	538	408	241	145	47
ZOL	899	846	730	555	414	257	123	54

	904	838	735	565	441	265	161	60
	899	851	744	573	434	270	131	59