

Systemic Adjuvant Therapy: What's the Best Approach?

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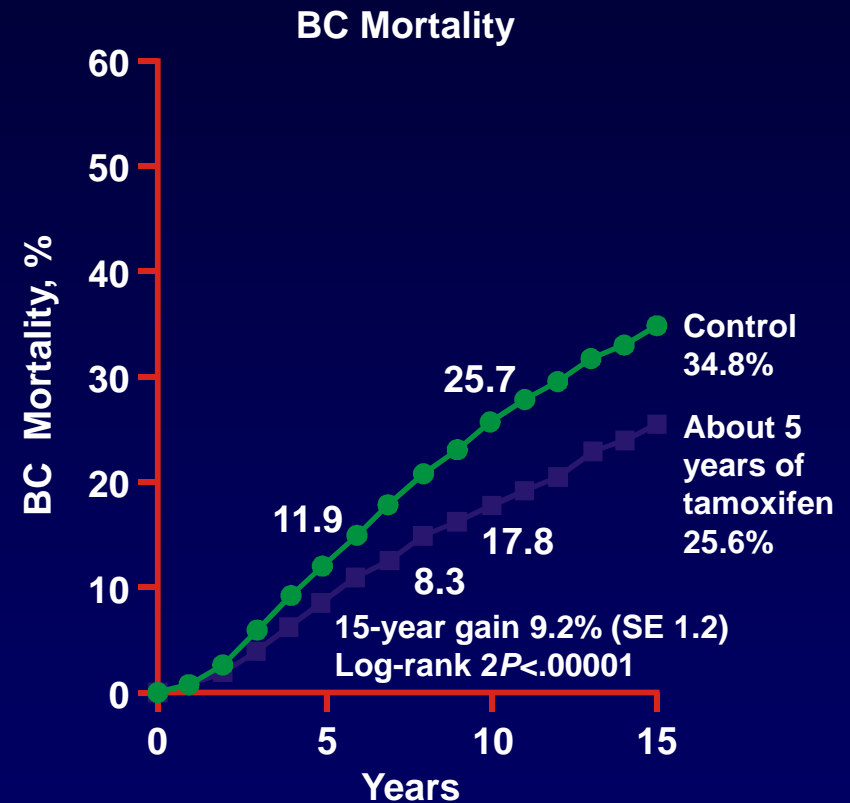
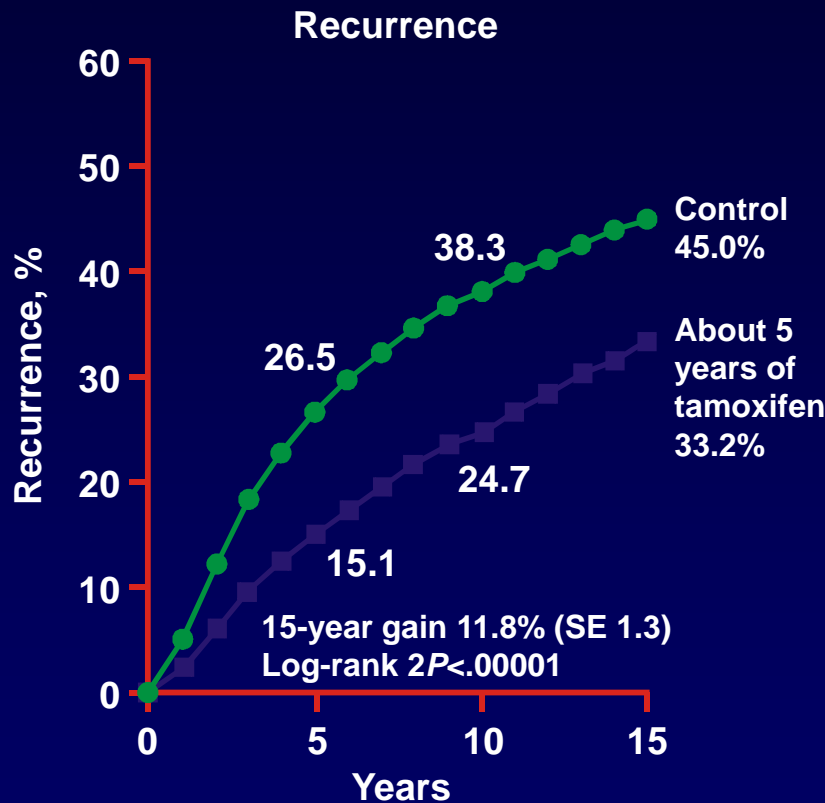
Texas Oncology, PA

Dallas, Texas

Choices

- TAM for 5 years or aromatase inhibitor (AI) for 5 years
- TAM 5 followed by AI 5 as initial plan: Lives will be lost
- AI followed by TAM—limited data
- TAM 2-3 years followed by AI

5 Years of Tamoxifen vs Not in ER+ (or ER-Unknown) Disease: 15-Year Probabilities of Recurrence and of Breast Cancer (BC) Mortality



10,386 women: 20% ER-unknown, 30% node-positive. Error bars are 1SE.

ATAC Trial Design: Phase III, Double-Blind, Randomized, Adjuvant Trial

N = 9366*

Patient stratification:

Node status

Prior CT

HR status

Diagnosis and
Initial Treatment
of EBC

R
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Anastrozole
1 mg PO qd × 5 years
(n = 3125)

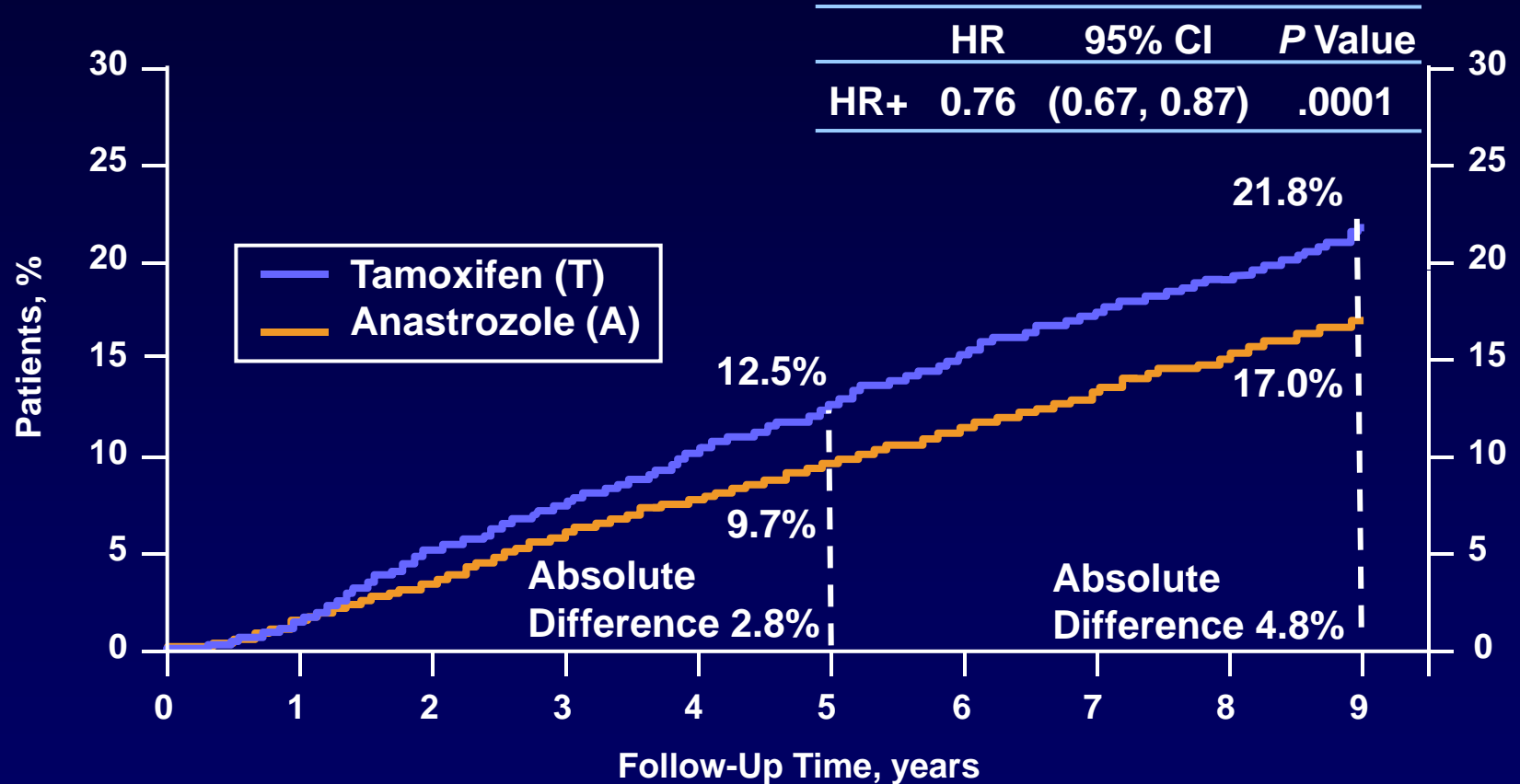
Tamoxifen
20 mg PO qd × 5 years
(n = 3116)

~~Combination
5 years
(n = 3125)~~

Disease-free survival
(DFS) HR = 0.87
(0.78-0.97; P = .01)

5 Years of Hormonal Therapy

ATAC: Time to Recurrence HR+ Patients

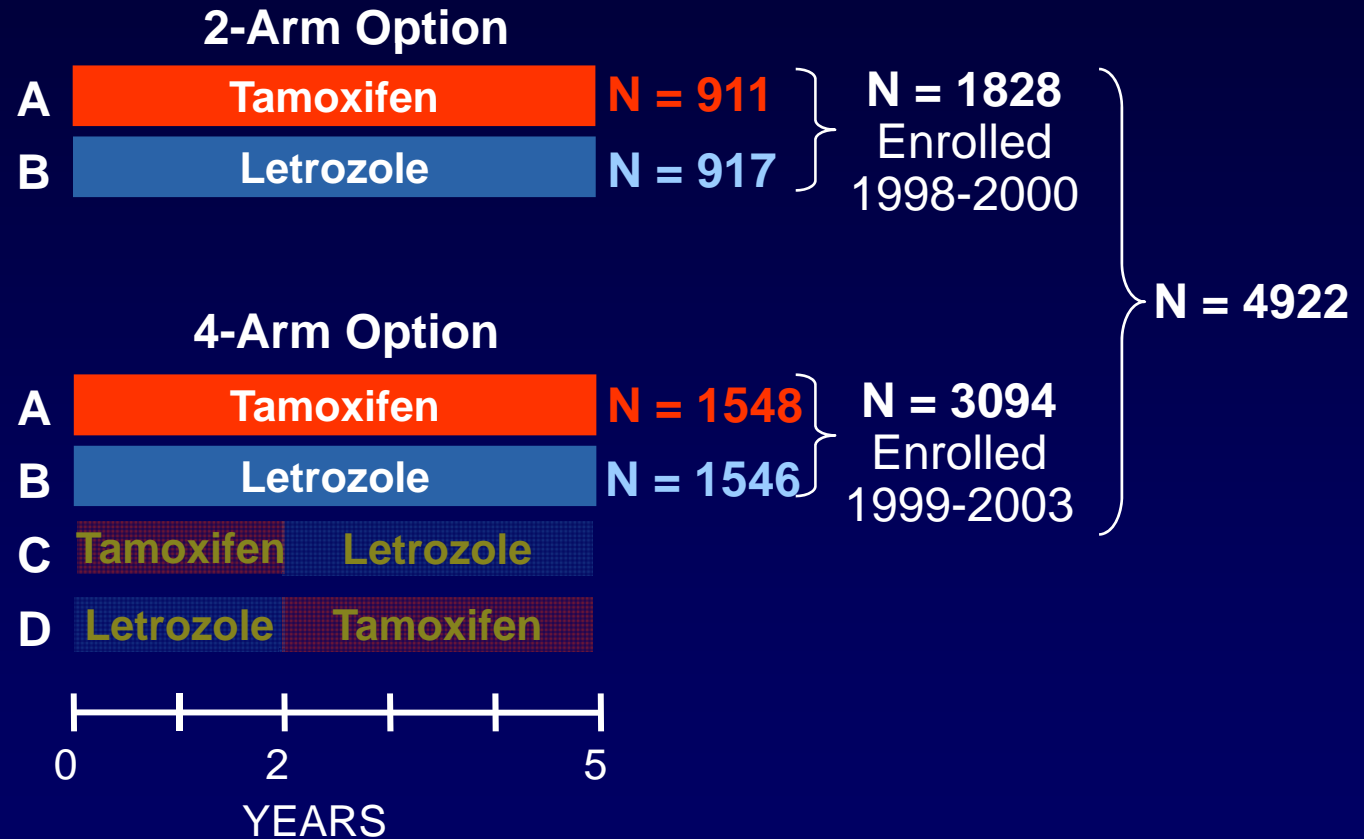


At risk:

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

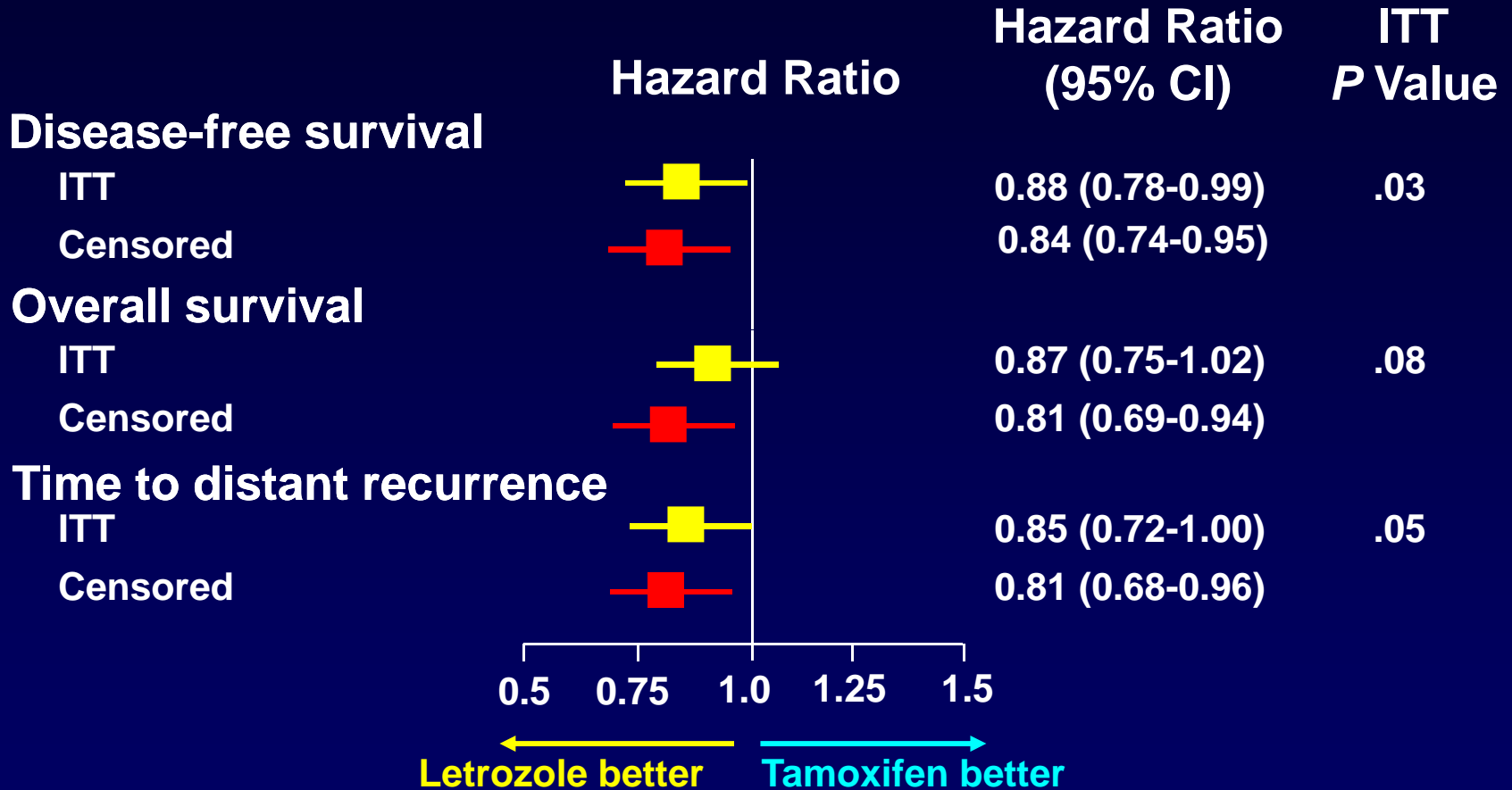
BIG 1-98 Monotherapy Update

Median Follow-Up 76 Months



BIG 1-98 Monotherapy Update

Median Follow-Up 76 Months



Letrozole:Tamoxifen: Breast cancer events, 321:363

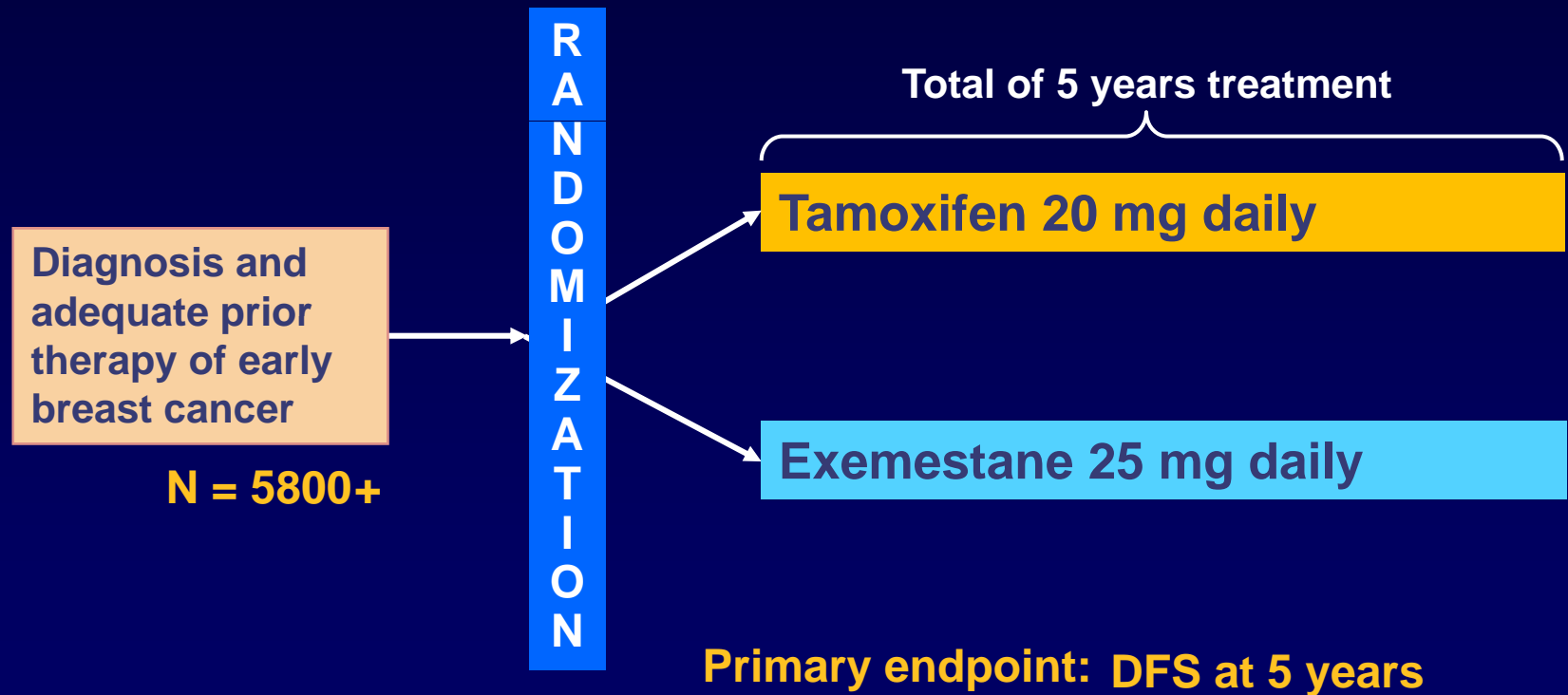
Second (nonbreast) malignancy, 101:115

Deaths without prior cancer event, 87:87



TEAM: Original Study Design (2001)

- Multinational, open-label, randomized study in postmenopausal, ER and/or PgR positive, early invasive breast cancer after completion of primary therapy

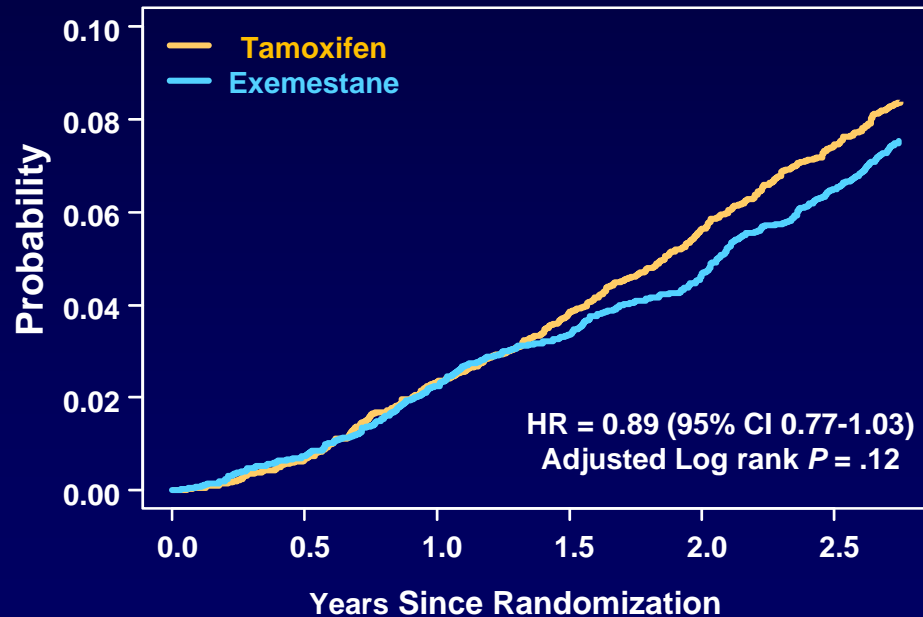




TEAM: DFS

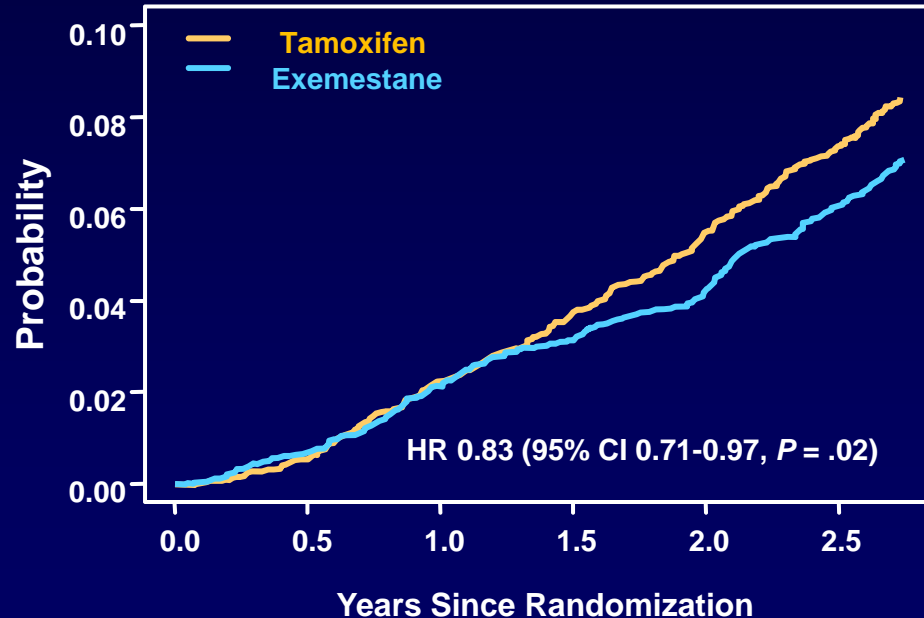
DFS at 2.75 Years (ITT)

Cumulative Probability



DFS: Censored

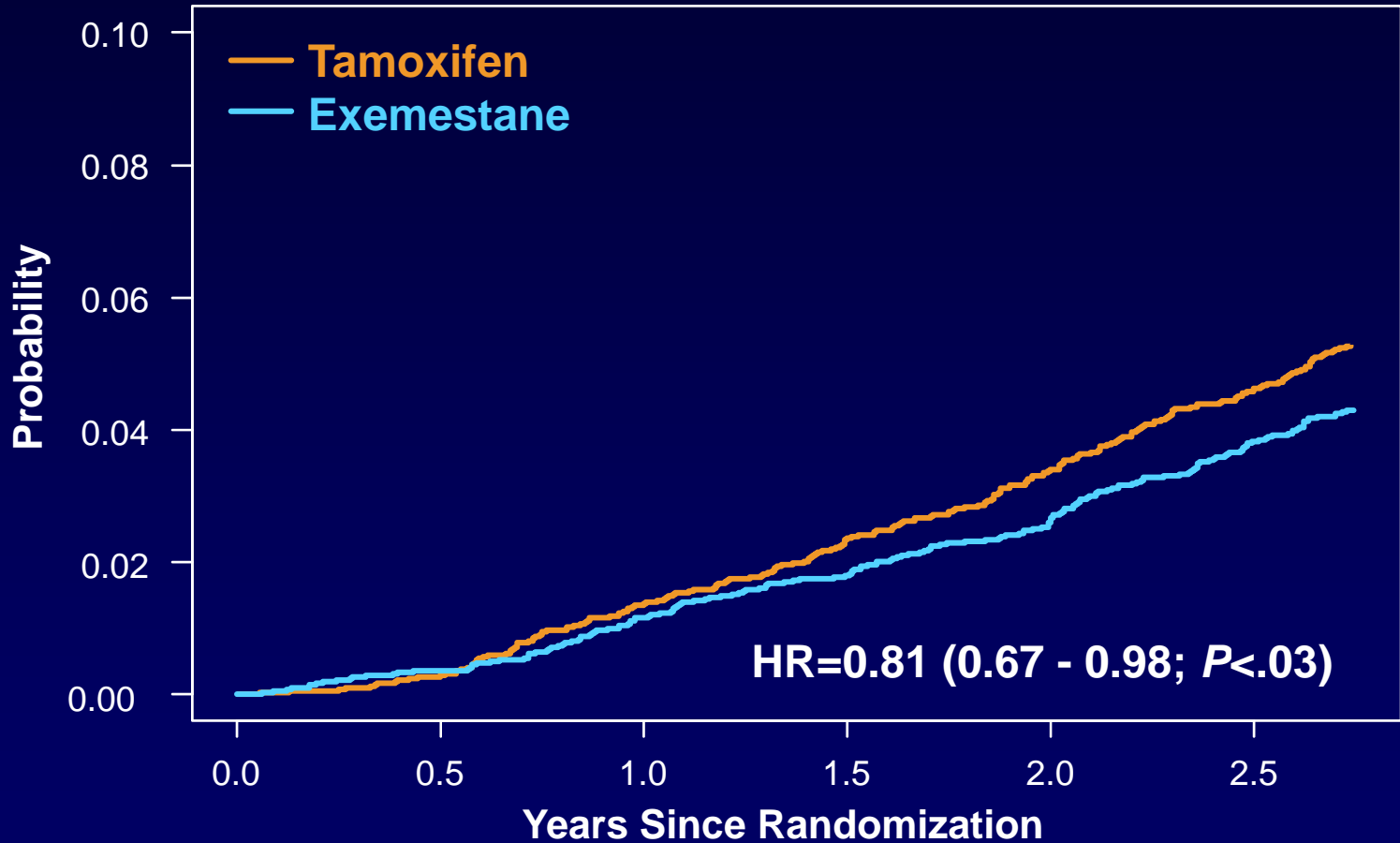
Cumulative Probability





Time to Distant Metastases (ITT)

Cumulative Incidence of Distant Metastasis (ITT)



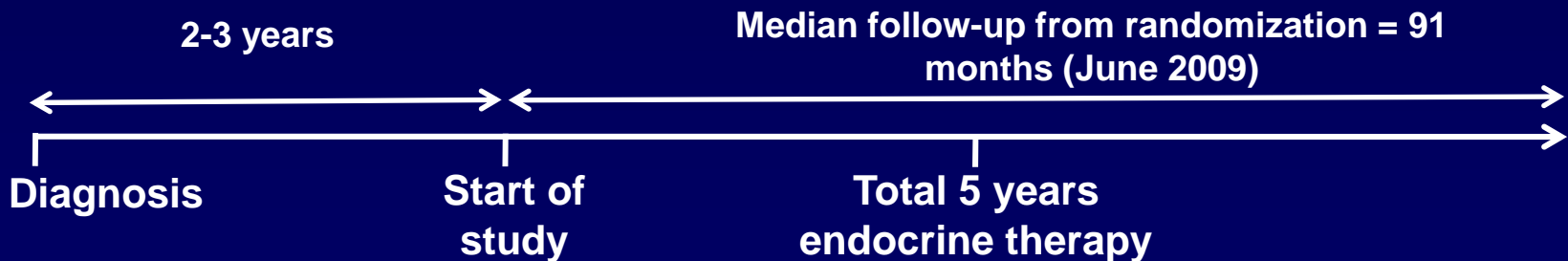
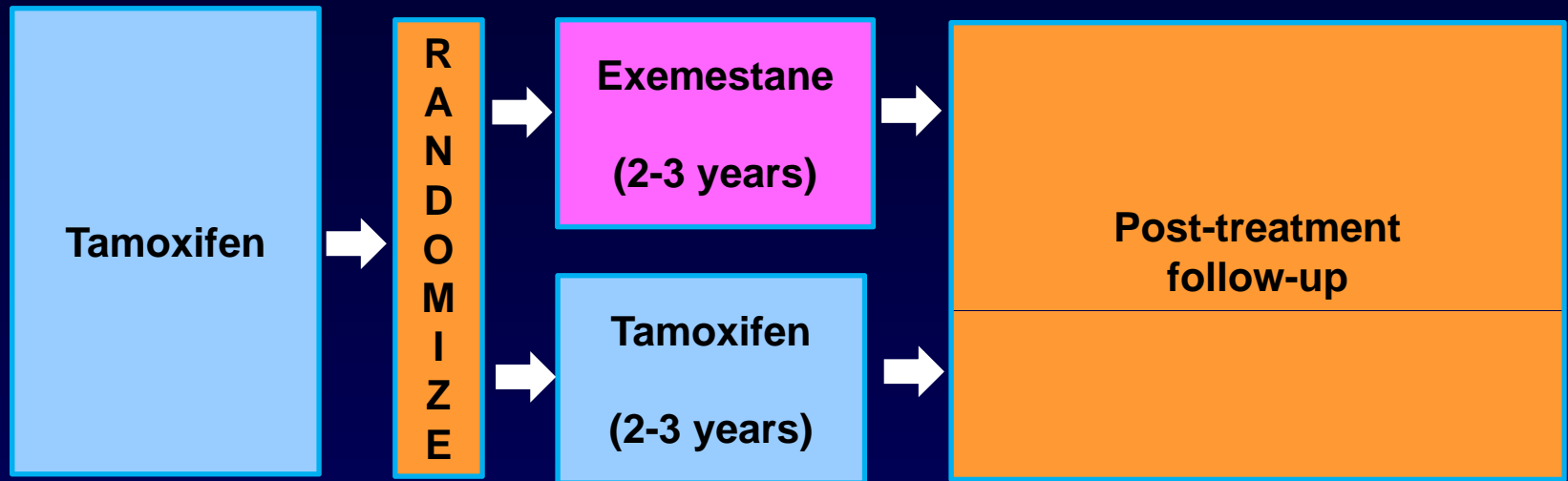
Numbers at risk:

Tamoxifen	4868	26/4771	69/4652	53/4547	71/4406	110/4146
Exemestane	4898	29/4815	54/4733	47/4646	56/4510	112/4219

TAM or AI for 5 Years?

- **3 large randomized trials show superiority of the AI over TAM in terms of DFS but not overall survival**
- **Safety profile better for the AI**
- **AI for 5 years is one clear choice**
- **What about TAM/AI for 5 years?**

IES: Exemestane After Tamoxifen

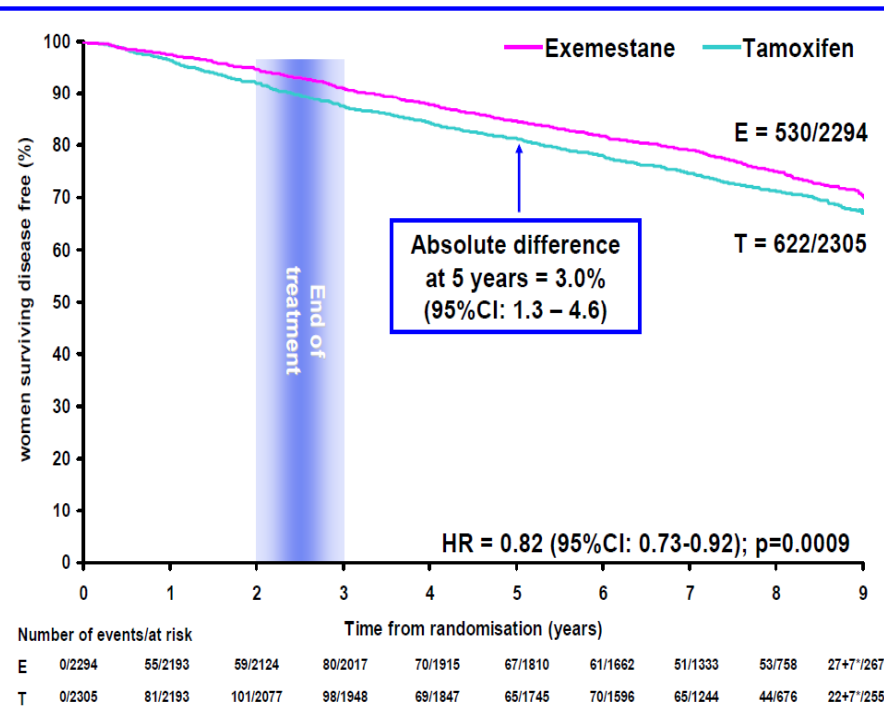


Total follow-up available from randomization at June 2009 analysis = 32296 women years

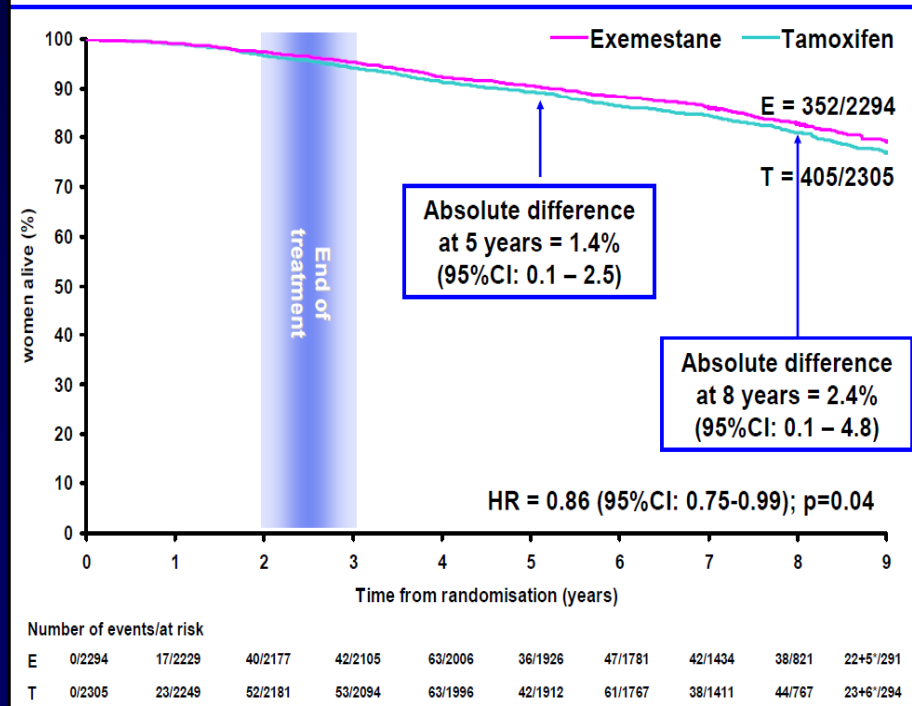
IES Update Median Follow-Up 91 Months

ER+ = 85.8%, ER unknown = 11.6%

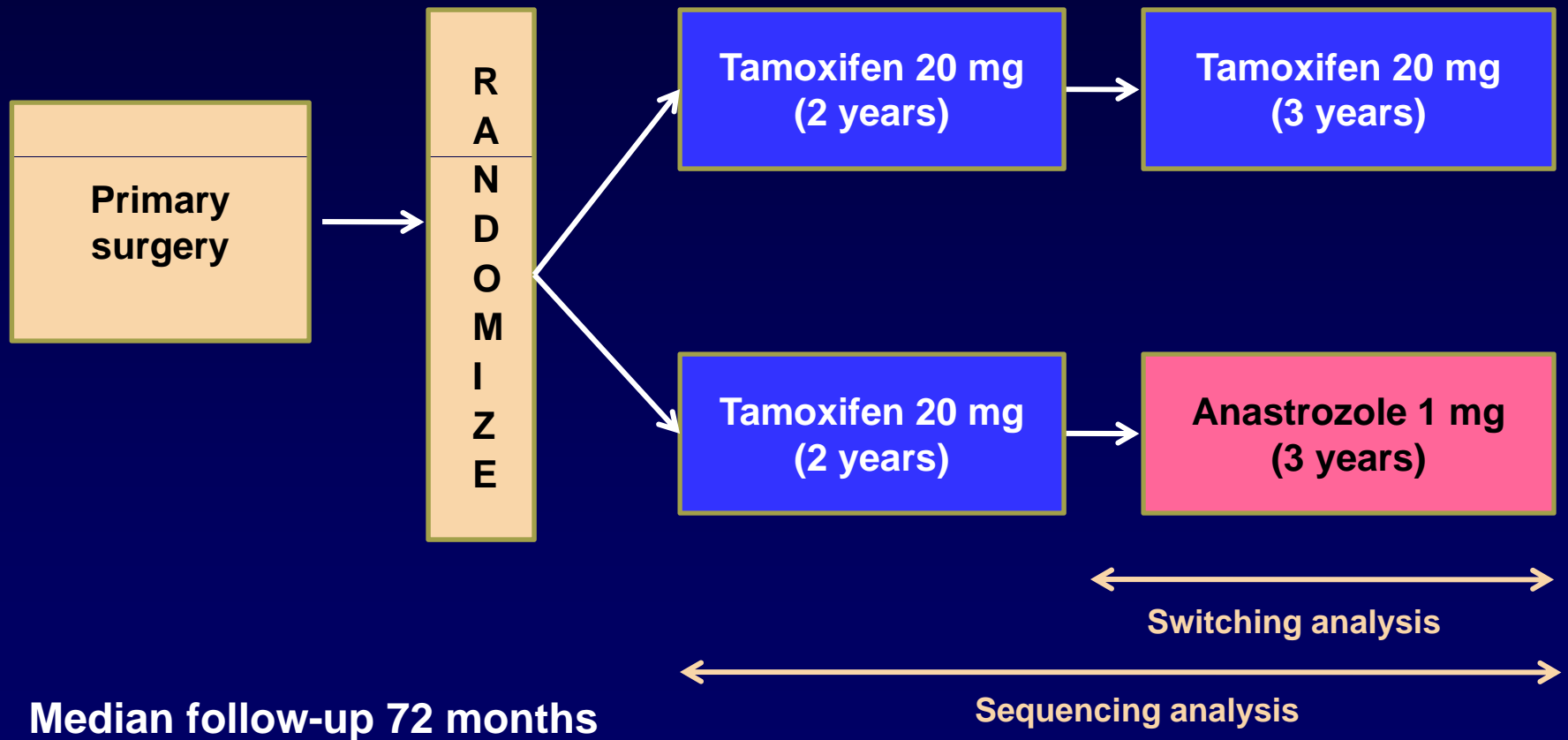
Disease Free Survival – ER+/unknown



Overall survival – ER+/unknown



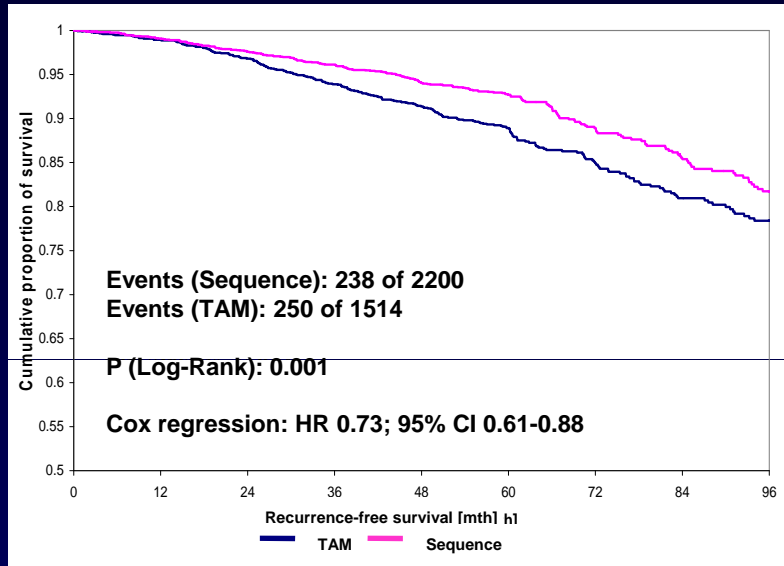
ABCSG Trial 8: Anastrozole After Tamoxifen



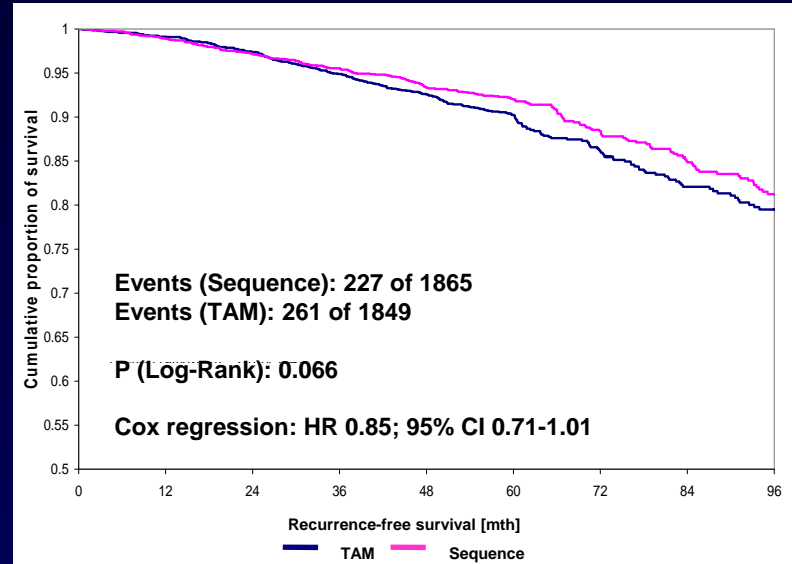
ABCESG Trial 8: RFS and OS

Total Sample

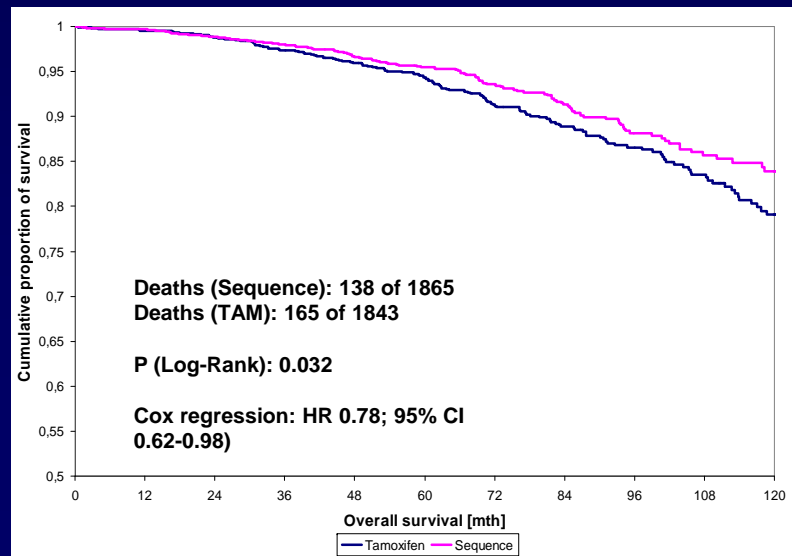
Retrospective: RFS



Cross-Over Censored: RFS and OS



RFS



OS

TAM/AI Switch

- **IES 91 month data: DFS and OS benefit persists**
- **ABC CSG 8: DFS and OS benefits**
- **ARNO: DFS and OS benefits**
- **WHAT ABOUT AI SWITCH TO TAM?**

BIG 1-98 Sequential Therapy Two Pairwise Comparisons

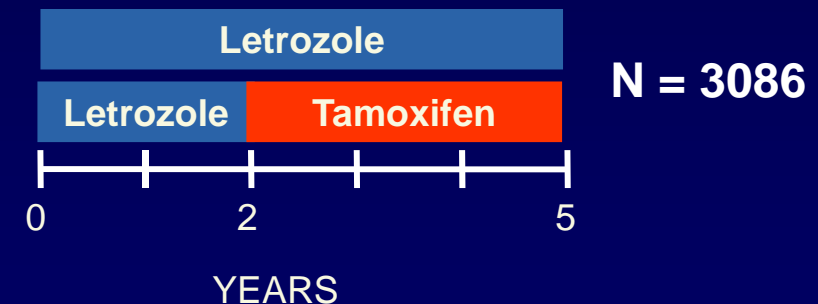
3 blinded arms

Sequential vs letrozole
monotherapy

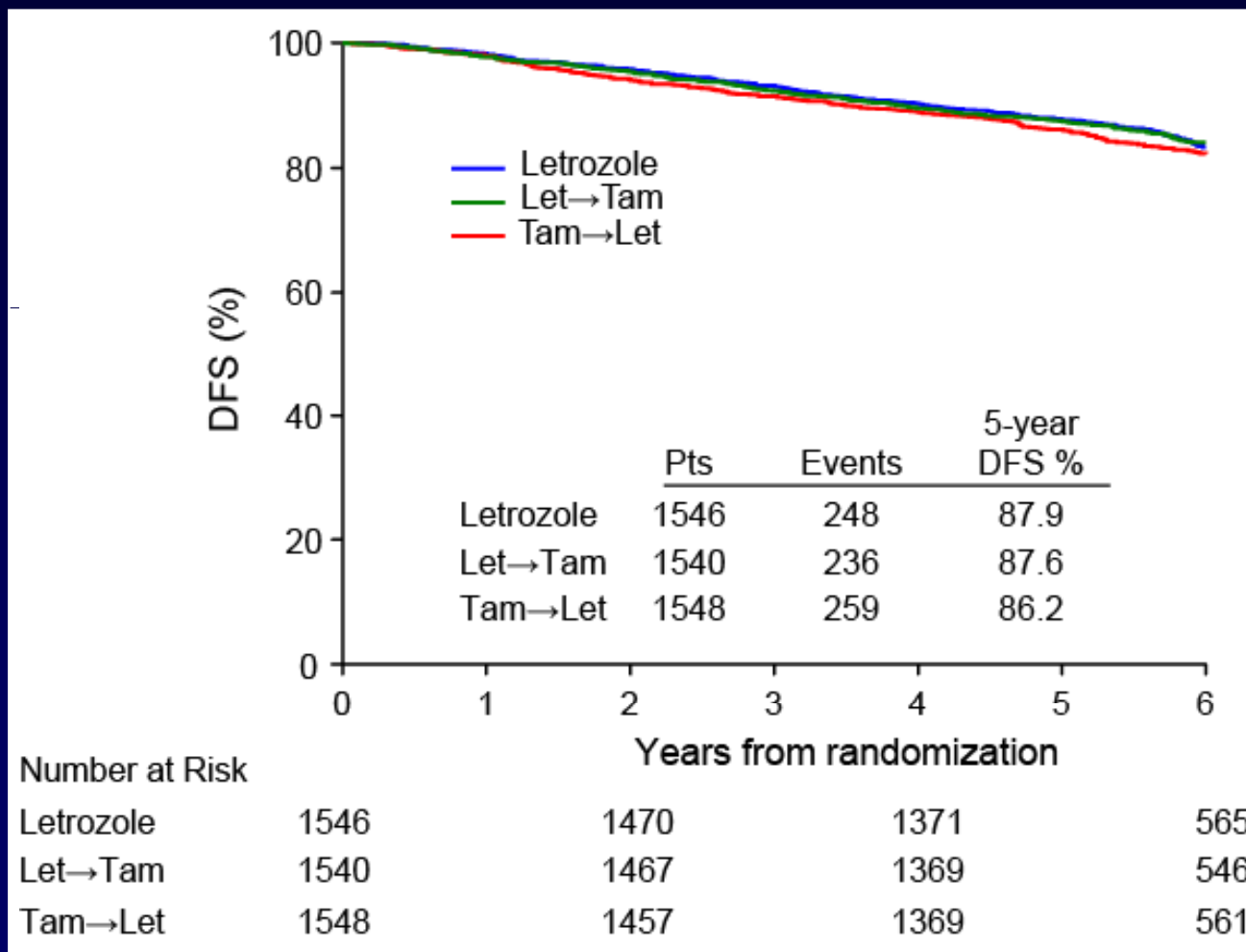
Evaluated from
randomization

Median Follow Up 71 months

99% confidence intervals to
account for multiple
comparisons



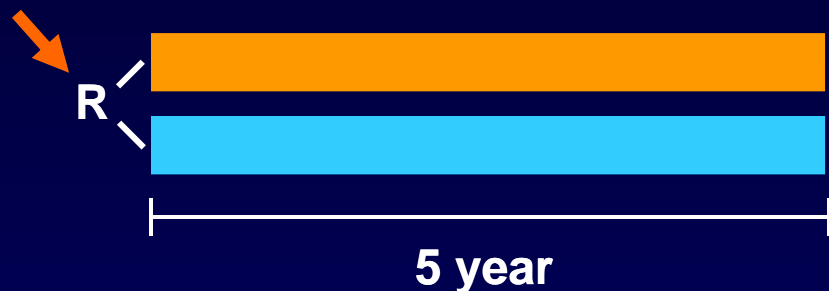
BIG 1-98 Sequential Therapy Disease-Free Survival



Comparison of Tamoxifen and an Aromatase Inhibitor Designs of *Cohort 1* and *Cohort 2*

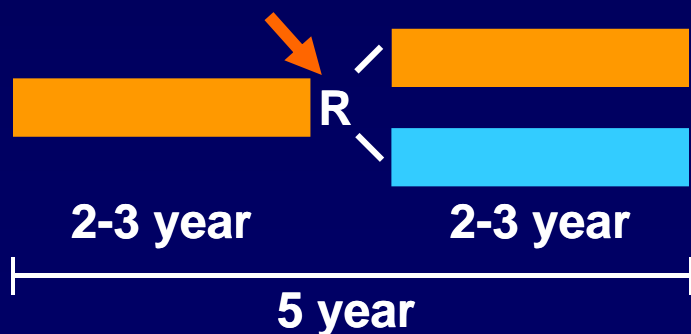
■ Tamoxifen ■ Aromatase inhibitor

Cohort 1: Direct comparison as monotherapy



Trials
ATAC
BIG 1-98/IBCSG 18-98

Cohort 2: Comparison after 2-3 years of tamoxifen

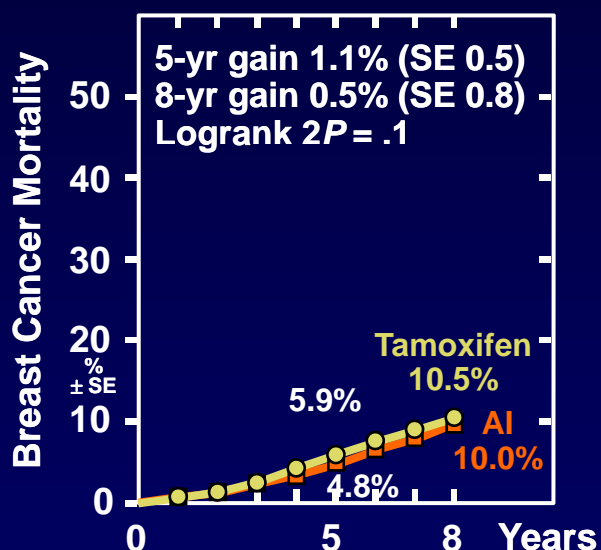


Trials
GABG/ARNO
IES/BIG 2-97
ITA
ABCSG VIII

Cohort 1:
Direct Comparison of
Tamoxifen and an Aromatase
Inhibitor (9856 Patients)

Cohort 1: Life-Table Curves of Breast Cancer Mortality, Death Without Recurrence and Any Death

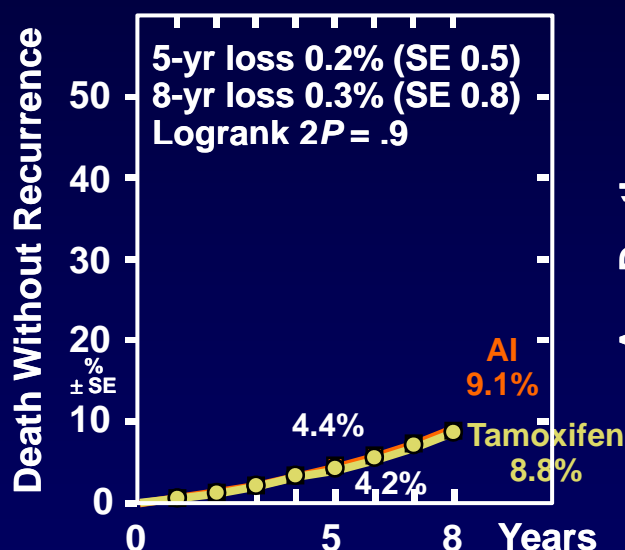
Breast Cancer Mortality



Death rates (%/year: total rate – rate in women without recurrence) & logrank analyses

	Years 0-1	Years 2-4	Years 5+
AI	0.59 SE 0.08	1.26 SE 0.10	1.78 SE 0.16
Tamoxifen	0.57 SE 0.08	1.60 SE 0.12	1.79 SE 0.16
Rate ratio, from (O-E)/V	1.01 SE 0.19	0.77 SE 0.10	1.01 SE 0.13
	0.2/27.5	-20.5/80.2	0.4/61.5

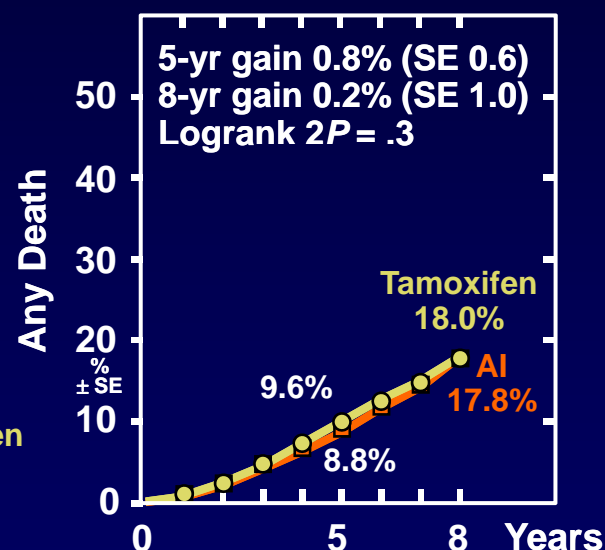
Death Without Recurrence



Death rate (%/year) and logrank analyses

	Years 0-1	Years 2-4	Years 5
AI	0.54 (52/9647)	1.10 (124/11297)	1.60 (110/6879)
Tamoxifen	0.59 (56/9510)	1.02 (112/10938)	1.62 (105/6478)
Rate ratio, from (O-E)/V	0.92 SE 0.19	1.07 SE 0.14	0.99 SE 0.14
	-2.1/26.8	4.1/58.3	-0.4/52.9

Any Death



Death rate (%/year) and logrank analyses

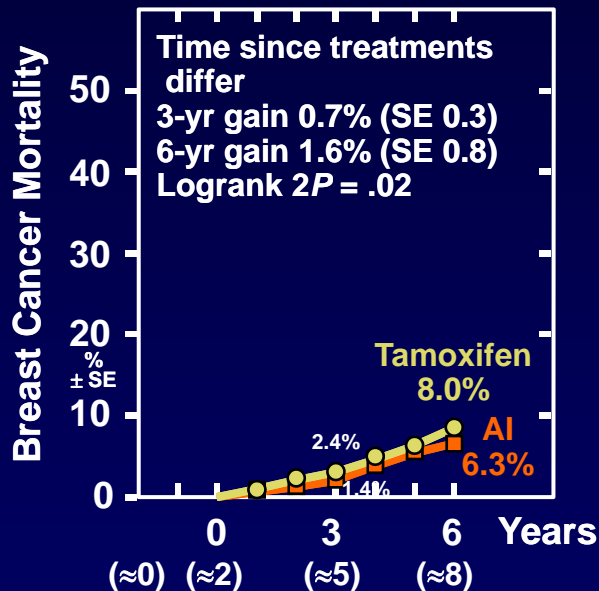
	Years 0-1	Years 2-4	Years 5+
AI	1.12 (109/9743)	2.31 (272/11757)	3.29 (240/7286)
Tamoxifen	1.15 (111/9656)	2.57 (297/11569)	3.26 (232/7107)
Rate ratio, from (O-E)/V	0.97 SE 0.13	0.89 SE 0.08	1.00 SE 0.09
	-1.9/54.3	-16.4/138.5	0.0/114.4

Cohort 2:

**Comparison of Tamoxifen and an
Aromatase Inhibitor After 2-3 Years
of Tamoxifen (9015 Patients)**

Cohort 2: Life-Table Curves of Breast Cancer Mortality, Death Without Recurrence and Any Death

Breast Cancer Mortality

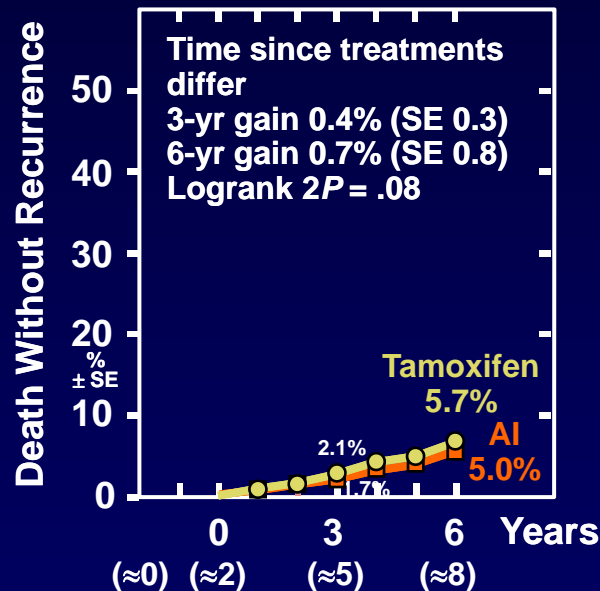


Time since allocated treatments differ (and approximate time since diagnosis)

Death rates (%/year: total rate – rate in women without recurrence) & logrank analyses

	Years 0-2 (≈2-4)	Years 3-5 (≈5-7)	Years 6+ (≈6+)
AI	0.54 SE 0.07	1.63 SE 0.17	1.17 SE 0.39
Tamoxifen	0.79 SE 0.08	1.85 SE 0.18	1.80 SE 0.48
Rate ratio, from (O-E)/V	0.68 SE 0.14 -13.9/36.5	0.89 SE 0.14 -5.4/46.4	0.65 SE 0.34 -2.5/5.7

Death Without Recurrence

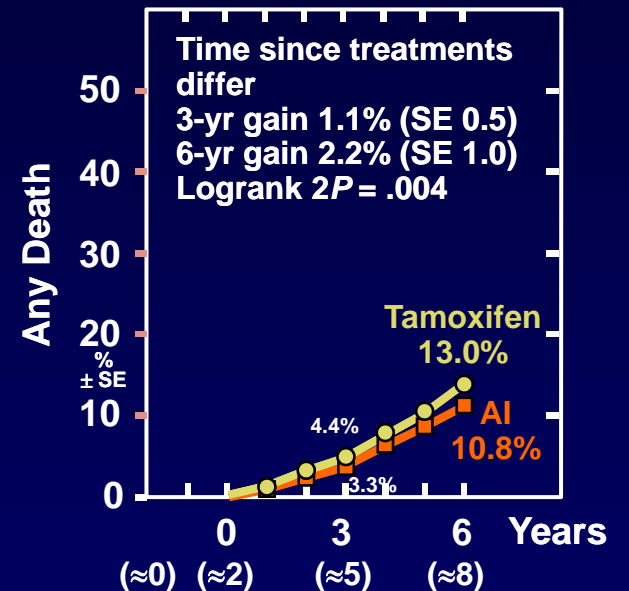


Time since allocated treatments differ (and approximate time since diagnosis)

Death rate (%/year) and logrank analyses

	Years 0-2 (≈2-4)	Years 3-5 (≈5-7)	Years 6+ (≈6+)
AI	0.57 (64/11134)	1.00 (53/5298)	1.12 (8/716)
Tamoxifen	0.70 (77/10962)	1.20 (60/5007)	1.58 (11/697)
Rate ratio, from (O-E)/V	0.82 SE 0.15 -7.0/35.0	0.83 SE 0.17 -5.3/27.9	0.68 SE 0.38 -1.8/4.7

Any Death



Time since allocated treatments differ (and approximate time since diagnosis)

Death rate (%/year) and logrank analyses

	Years 0-2 (≈2-4)	Years 3-5 (≈5-7)	Years 6+ (≈6+)
AI	1.11 (125/11300)	2.59 (144/5566)	2.20 (17/771)
Tamoxifen	1.47 (166/11301)	2.95 (161/5455)	3.22 (25/776)
Rate ratio, from (O-E)/V	0.75 SE 0.10 -20.9/71.5	0.87 SE 0.11 -10.7/74.2	0.66 SE 0.25 -4.3/10.3

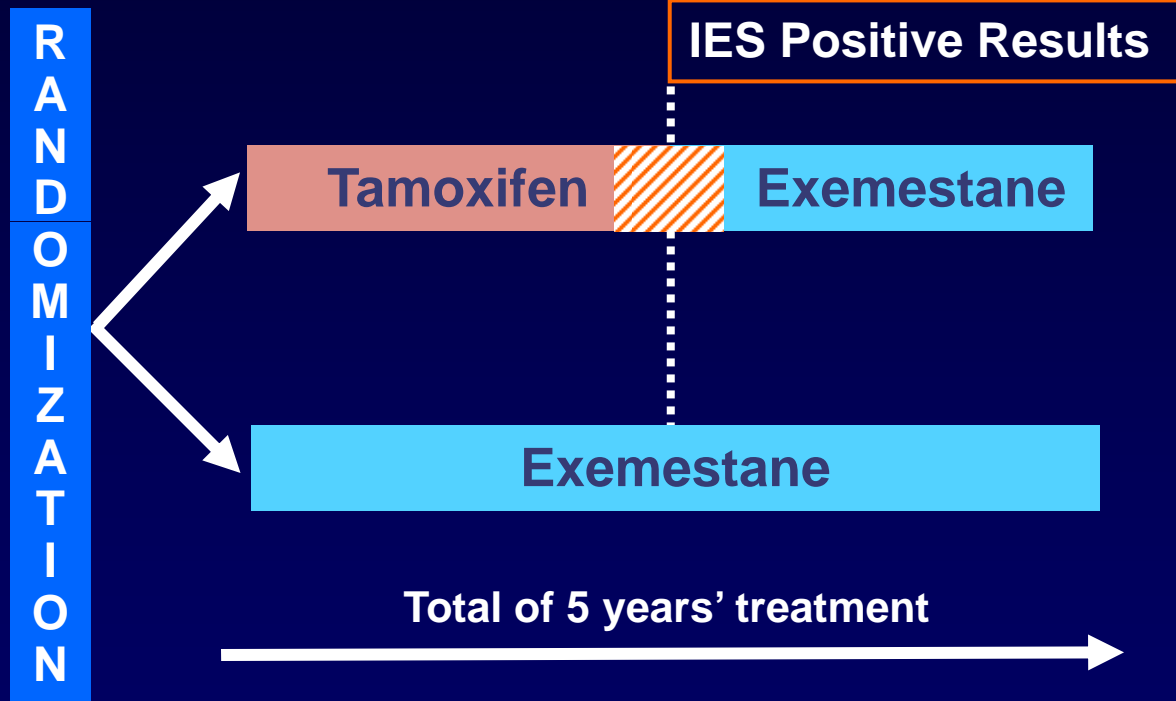


TEAM Trial: Revised Design 2004

N = 9775 accrued

Postmenopausal
receptor-positive
women

Diagnosis and
adequate
primary therapy
of early breast
cancer



Co-primary end points

DFS at 2.75 years
DFS at 5 years

Conclusions

AI for 5 years well supported by studies

TAM/AI switch well supported by studies and has associated overall survival benefit

- **For most patients little or no risk of recurrence in the first 2 years of TAM**
- **Cost effective**
- **Benefit of 2 effective agents**
- **Ideal in women of questionable postmenopausal status**
- **Suited for longer term treatment**
- **My preferred treatment for the patient under discussion**

THANK YOU