

# Letrozole Monotherapy vs. Tamoxifen Monotherapy or vs. Letrozole in Sequence with Tamoxifen for Postmenopausal Women with Endocrine-Responsive Early Breast Cancer

**BIG 1-98/IBCSG 18-98**

*Henning Mouridsen*

*for the **BIG 1-98 Collaborative Group***

*Coordinated by the*

***International Breast Cancer Study Group***



International Breast Cancer Study Group


**IBCSG SABCS 2008**



# Disclosure

- BIG 1-98 is coordinated by the International Breast Cancer Study Group and financed by Novartis
- Henning Mouridsen has received fees from Novartis for advisory boards and lectures

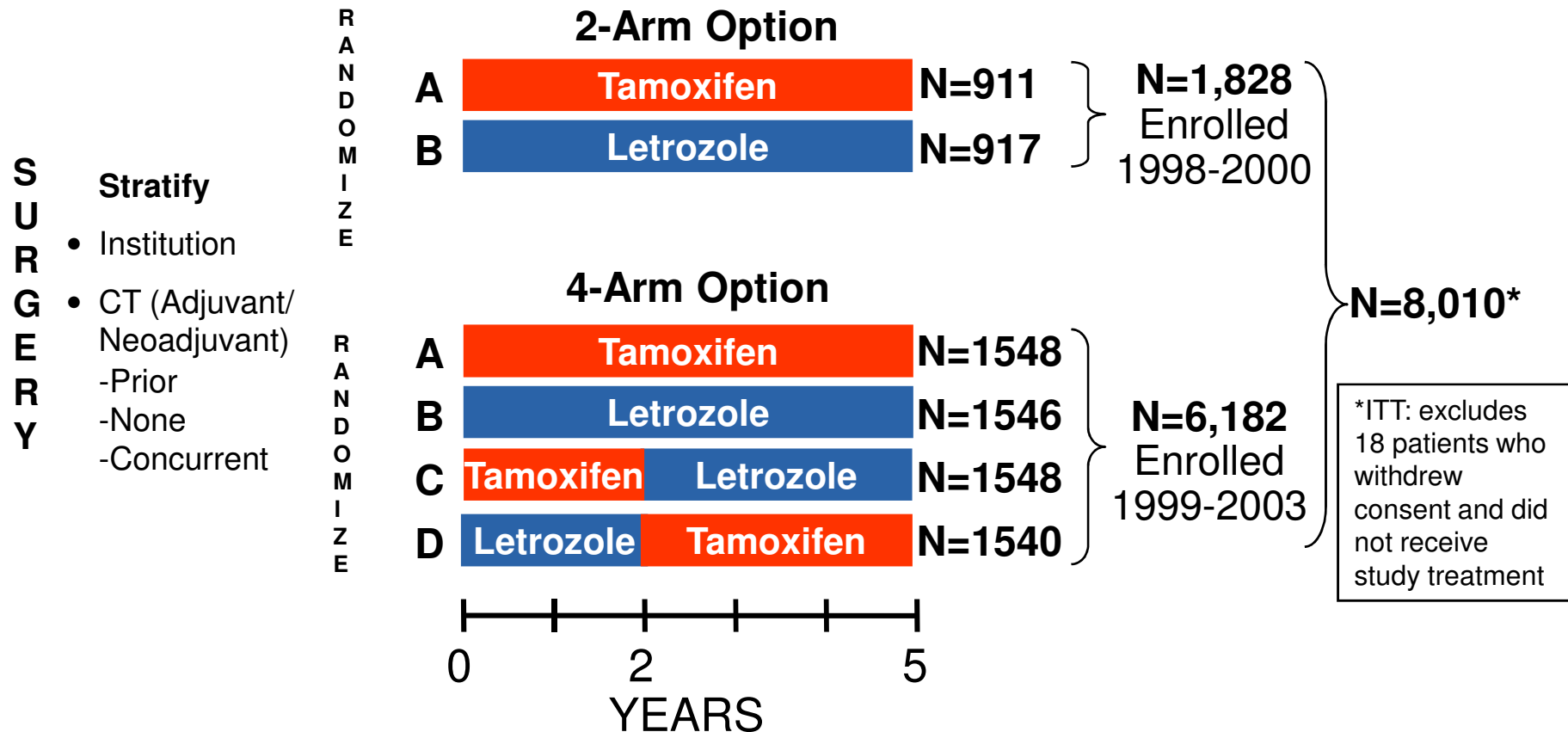
# BIG 1-98 Worldwide Collaborative

A world map with a light gray background. Countries that are part of the BIG 1-98 Worldwide Collaborative are highlighted in a light pink color. These include Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Rep., Denmark, France, Germany, Hungary, Iceland, Italy, Netherlands, New Zealand, Peru, Poland, Portugal, Russia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, United Kingdom, and Uruguay.

Argentina	123
Australia	667
Belgium	634
Brazil	17
Canada	20
Chile	22
Czech Rep.	109
Denmark	1396
France	1016
Germany	113
Hungary	334
Iceland	6
Italy	1285
Netherlands	94

New Zealand	157
Peru	51
Poland	277
Portugal	64
Russia	240
Slovenia	15
South Africa	187
Spain	70
Sweden	64
Switzerland	611
Turkey	54
United Kingdom	401
Uruguay	1
<b>TOTAL</b>	<b>8028</b>

# BIG 1-98 Overall Design



Previous Analyses:

**Is 5 years Let superior to 5 years Tam as initial therapy?**

- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months



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# Summary of Previous Analyses

The PCA and monotherapy analyses showed that 5 years upfront letrozole is significantly superior to 5 years of upfront tamoxifen in terms of

- Disease-Free Survival
- Time to Distant Recurrence

*BIG 1-98 Collaborative Group, N Engl J Med 2005;353:2747-57*

*Coates et al, J Clin Oncol 2007;25:486-92*

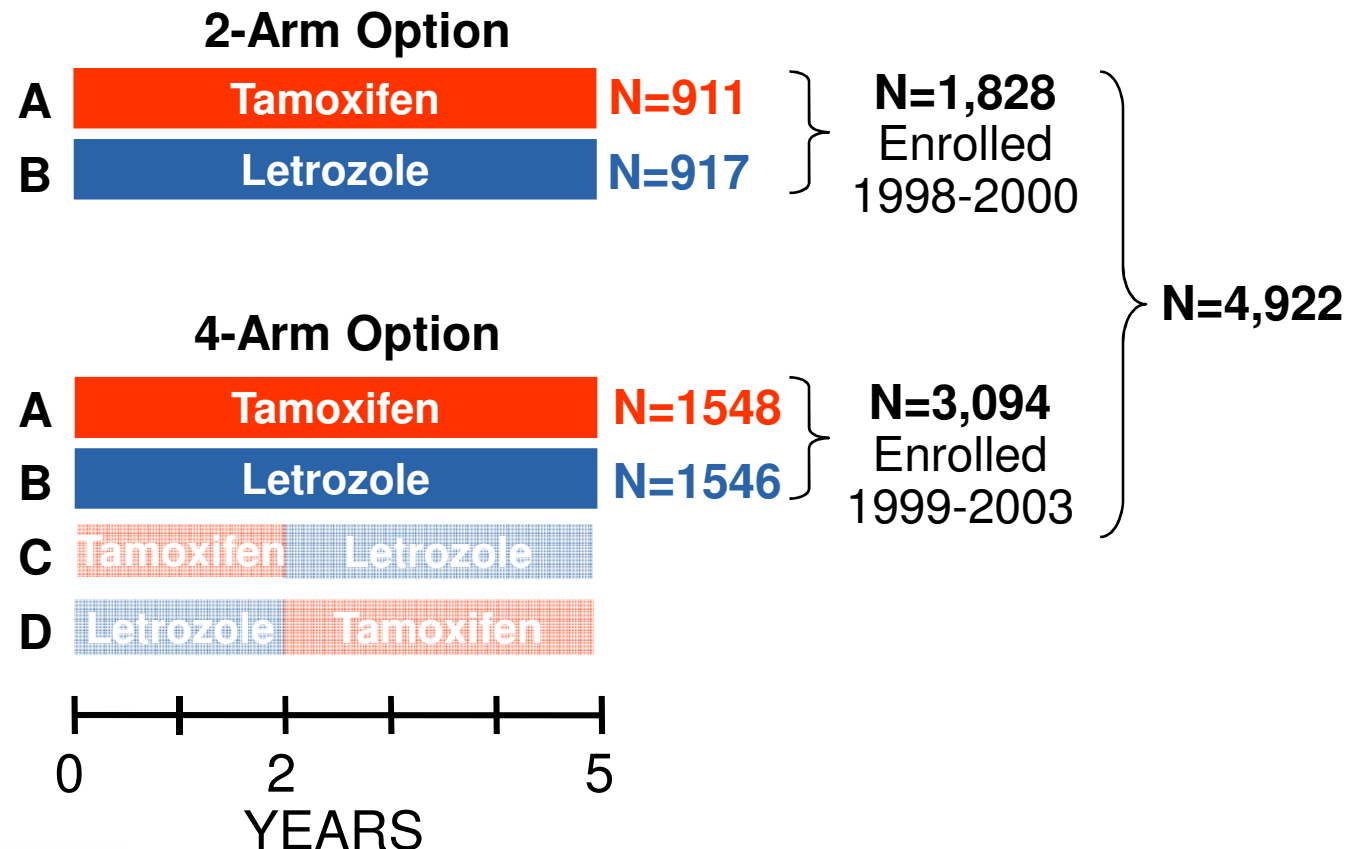
# BIG 1-98

## New Data to Be Presented

- Monotherapy update
  - Protocol-specified, 10-years from start of study
  - Median follow-up 76 months
- Sequential therapy vs. letrozole
  - Protocol-specified final efficacy analysis (DSMC October 2008)
  - Median follow-up 71 months

# BIG 1-98 Monotherapy Update

## Median Follow-up 76 months



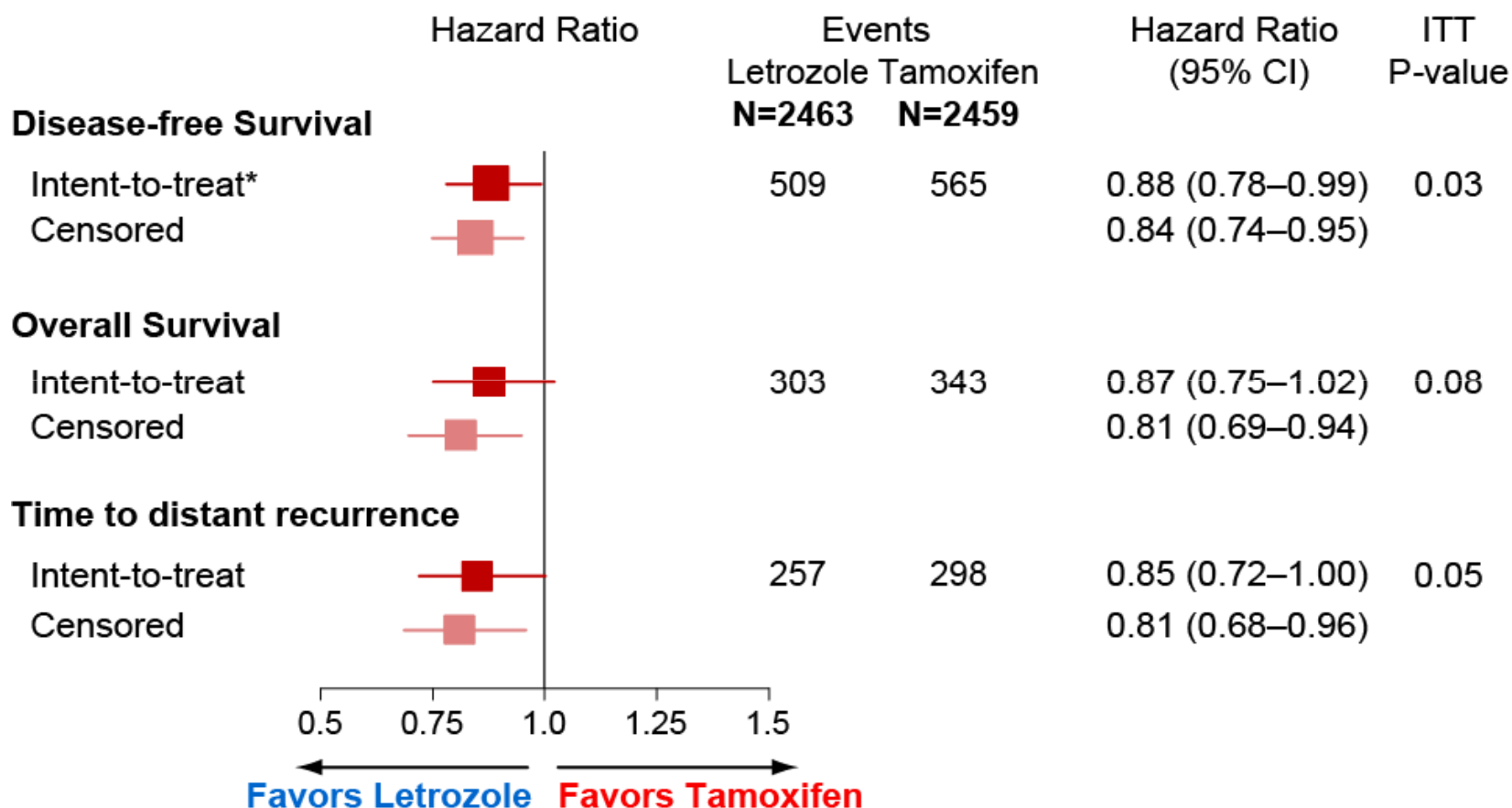
# BIG 1-98 Monotherapy Update

- 2005 results of Let superiority led to unblinding of Tam-alone arm
- 619 (25.2%) patients selectively crossed over to Let
  - Mostly in years 3-5
  - Median duration Let after crossover 18 mos.
- This complicates comparisons with Tam alone
- The comparison of Tam vs. Let was done by
  - Intent-to-treat (ITT)
  - Censoring at crossover



# BIG 1-98 Monotherapy Update

## Median Follow-up 76 months



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\*Let:Tam: breast cancer events, 321:363  
second (non breast) malignancy, 101:115  
deaths without prior cancer event, 87:87

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# BIG 1-98

## New Data to Be Presented

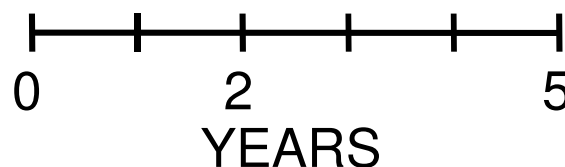
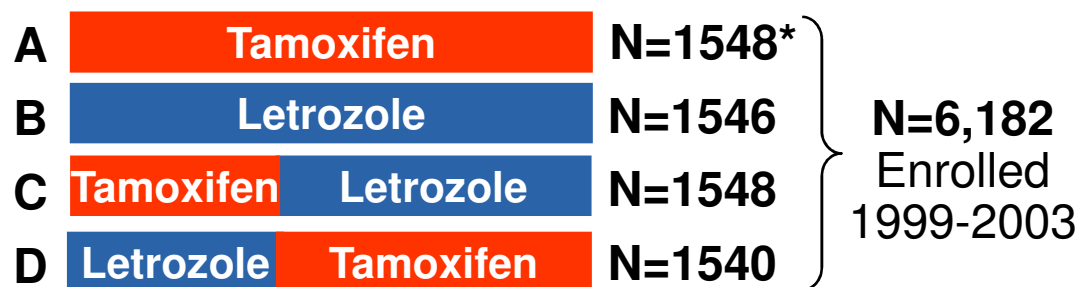
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# BIG 1-98 Sequential Therapy

## 2-Arm Option



## 4-Arm Option



\*612 patients (39.5%) selectively crossed over to letrozole after the tamoxifen arm was unblinded. The present analysis includes only 3 blinded arms (B, C, D)



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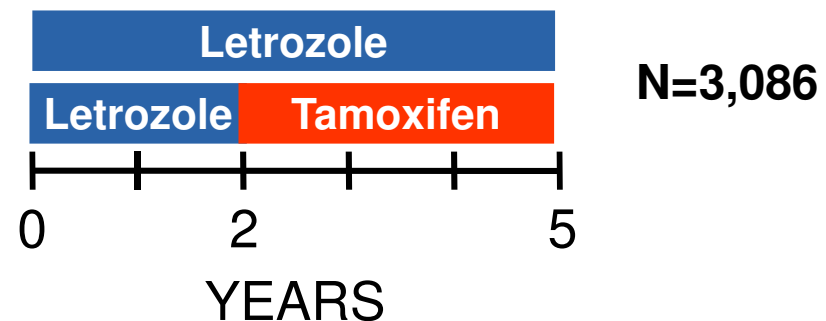
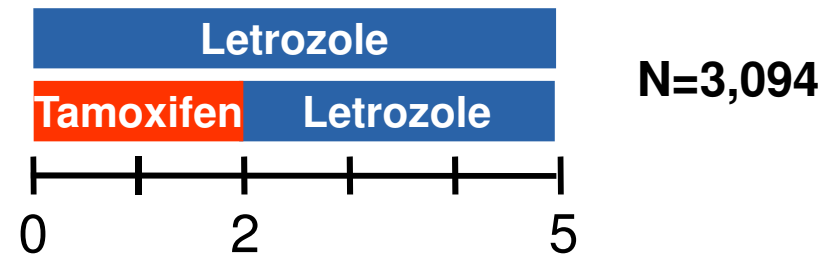
**Is a sequence of agents superior to letrozole monotherapy?**

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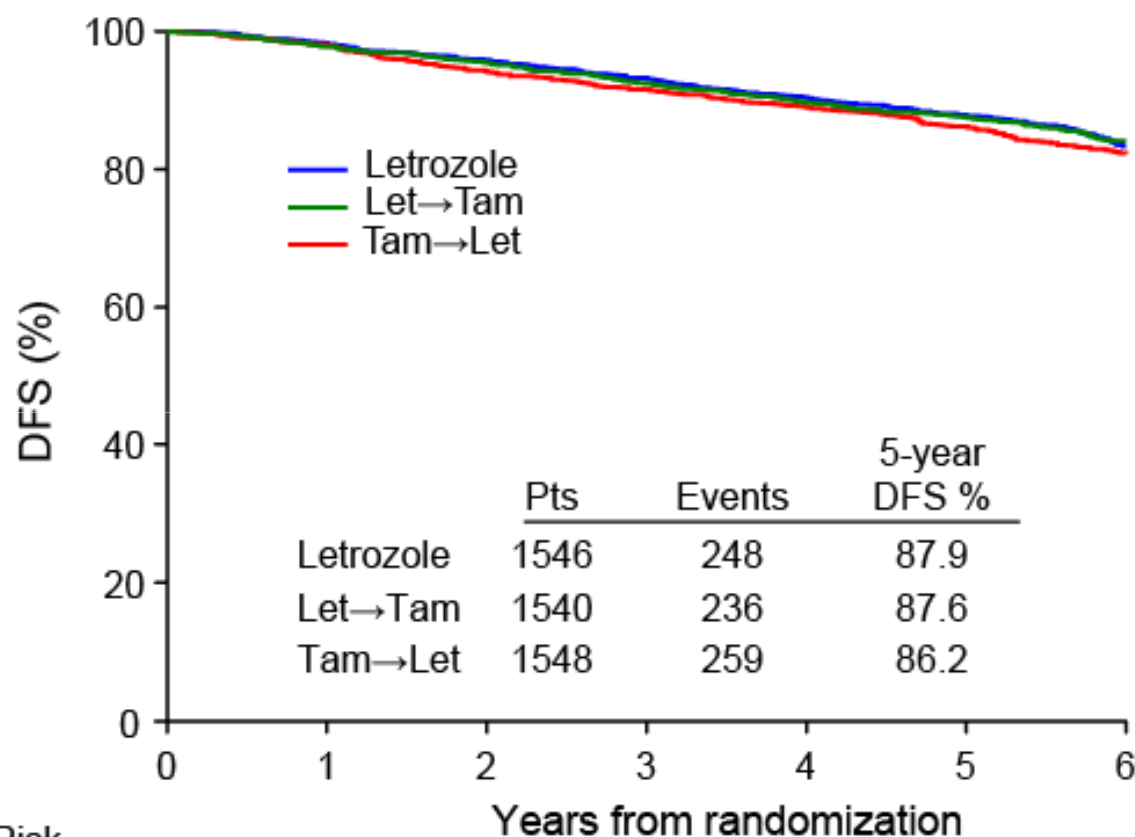
# BIG 1-98 Sequential Therapy

## Two Pairwise Comparisons

- 3 blinded arms
- Sequential vs. letrozole monotherapy
- Evaluated from randomization
- Median Follow Up 71 mos.
- 99% confidence intervals to account for multiple comparisons



# BIG 1-98 Sequential Treatment Disease-Free Survival



Number at Risk

Letrozole	1546	1470	1371	565
Let→Tam	1540	1467	1369	546
Tam→Let	1548	1457	1369	561



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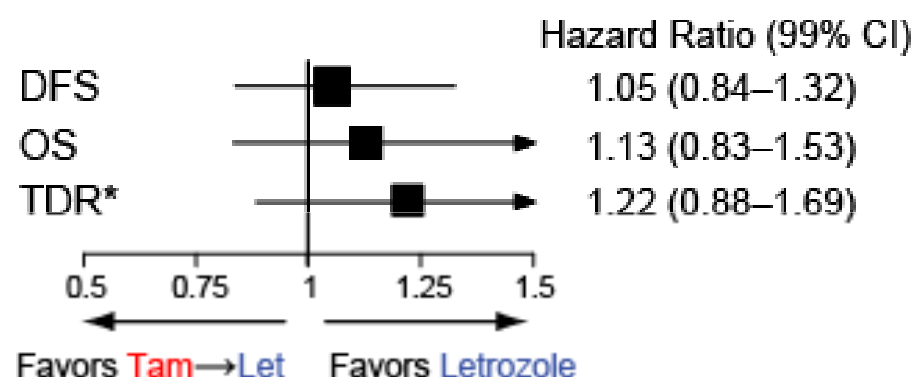
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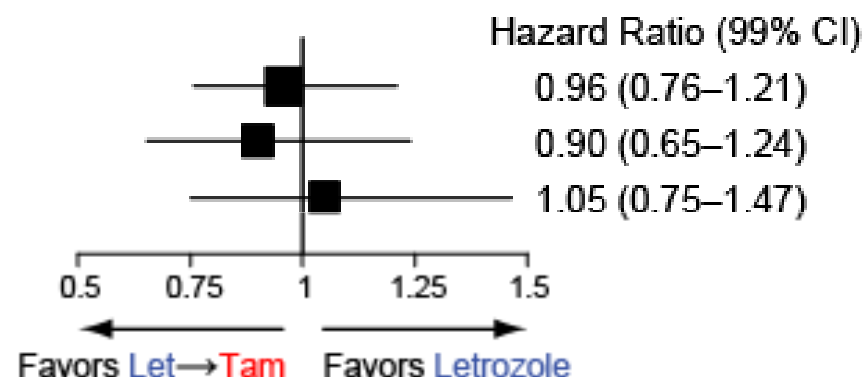
# Sequential Treatment Comparisons

## Median Follow-up 71 months

### Tam→Let vs. Let



### Let→Tam vs. Let



\*Time to distant recurrence



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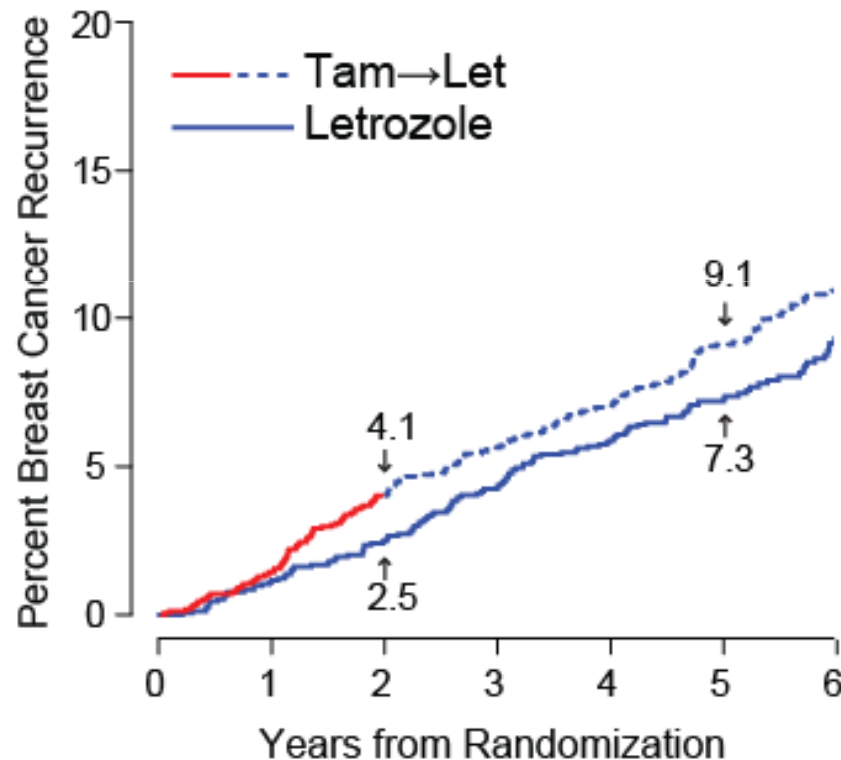
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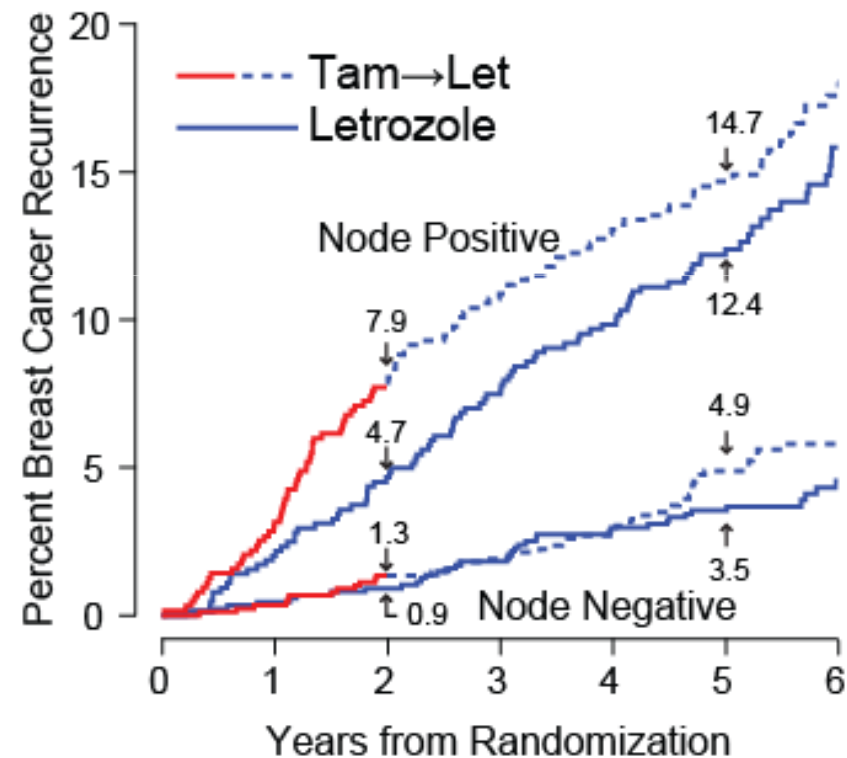
# Breast Cancer Events

Tam→Let vs. Let

Overall



By Nodal Status\*



\*42% of the population is node positive; 58% node negative



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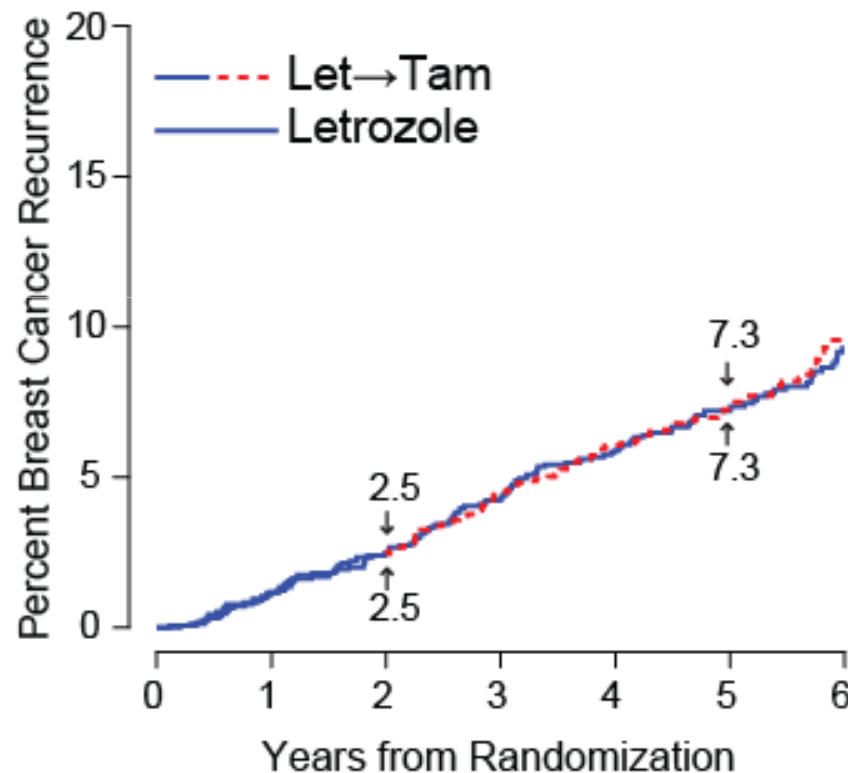
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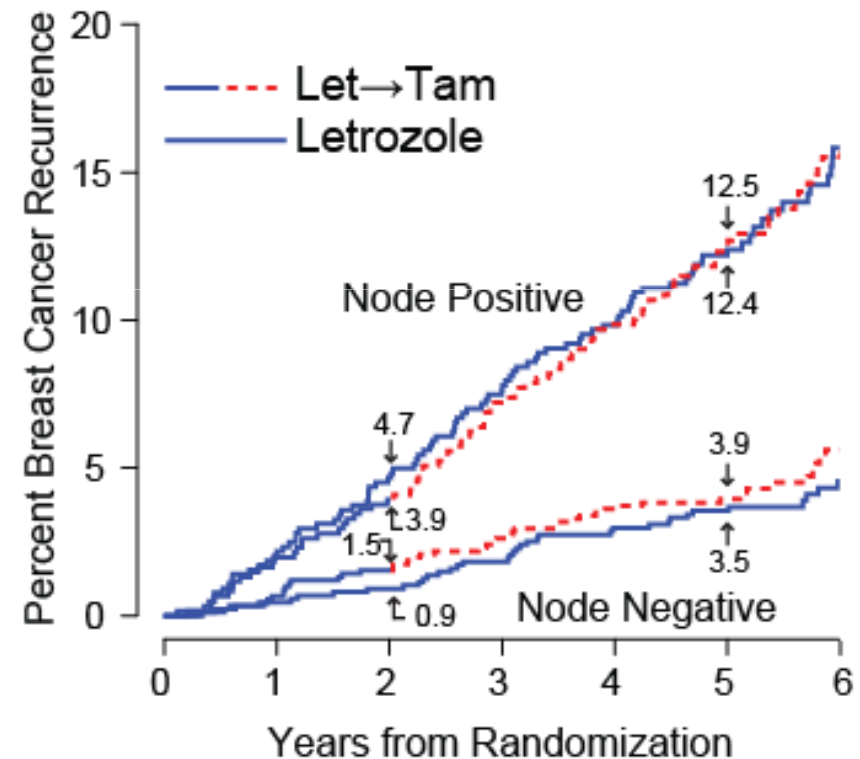
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Let→Tam vs. Let

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# Conclusions

For postmenopausal women with endocrine-responsive breast cancer

- Updated results of BIG 1-98 suggest superior overall survival with letrozole compared with tamoxifen
- Adjuvant endocrine therapy should start with letrozole especially for patients at higher risk for early recurrence
- Patients commenced on letrozole can be switched after 2 years to tamoxifen, if required
- Safety is consistent with known safety profiles of each agent (data not shown)
- Improved therapeutic approaches beyond five years are required to control late relapses

# Thanks to...

- The patients participating in the trial
- The principal investigators
- The co-investigators, data managers, nurses, study coordinators
- The cooperative groups
- The IBCSG Data and Safety Monitoring Committee
- The trial monitors/audit teams
- Novartis

# BIG 1-98 Investigators Meeting

December 10, 2008

San Antonio, Texas

