BIG 1-98: Where do we stand ?

BIG 1-98/IBCSG 18-98

Beat Thürlimann

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

Coordinated by the

International Breast Cancer Study Group

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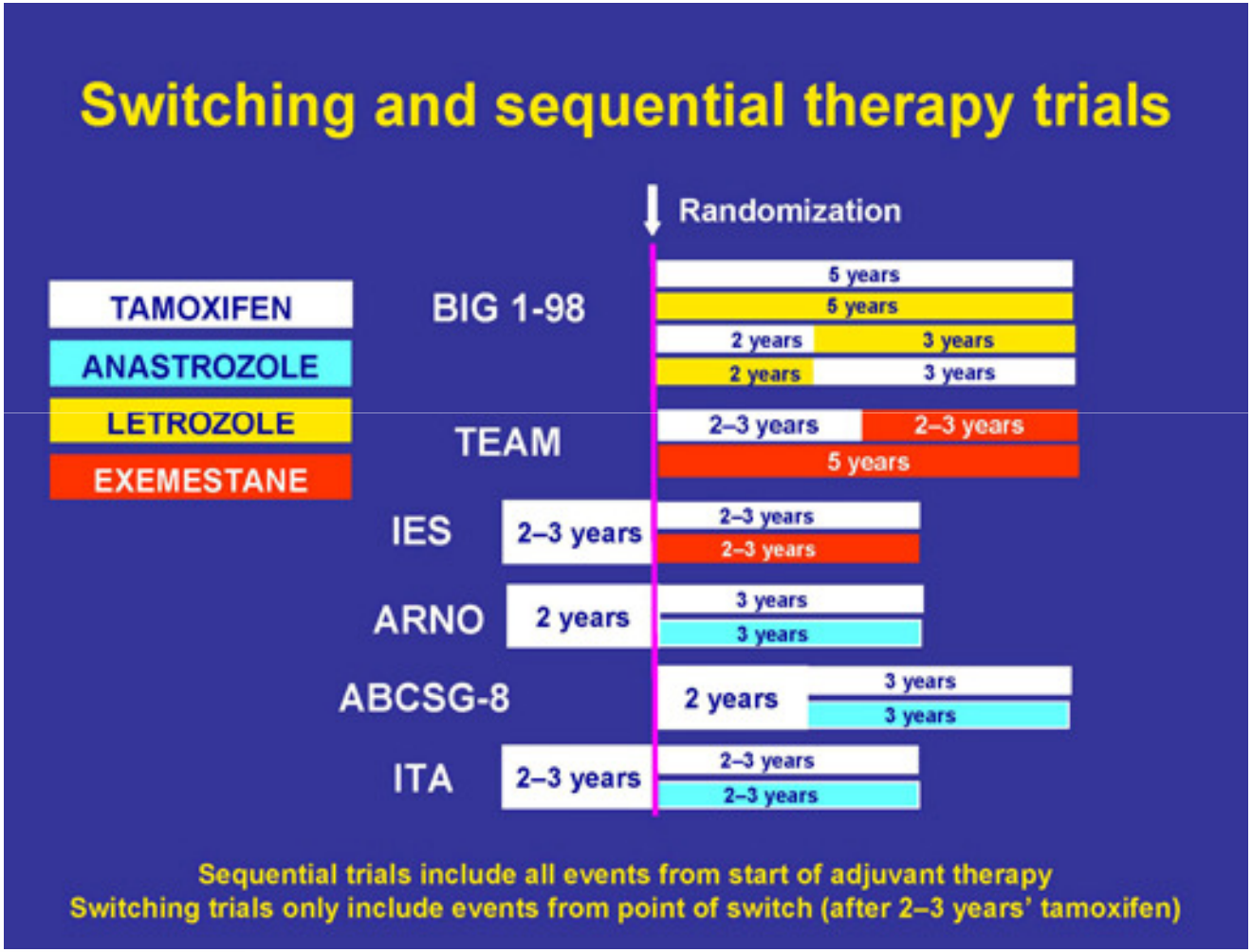
Disclosure

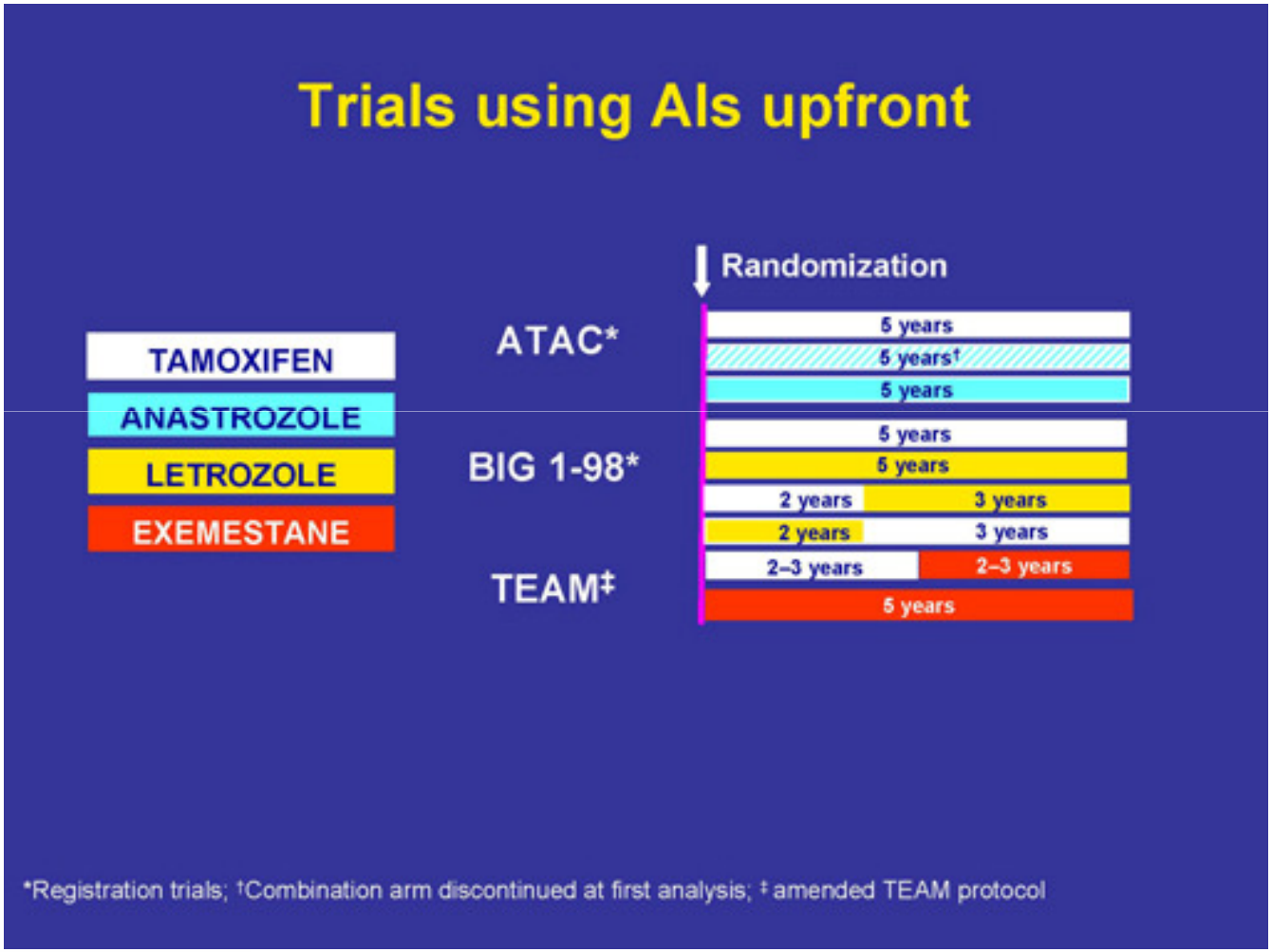
- BIG 1-98 is coordinated by the

  International Breast Cancer Study Group and financed by Novartis
- Beat Thürlimann owns stock of Novartis
- Beat Thürlimann has not received honoraria or consultation fees from Novartis

Aromatase Inhibitor Trials



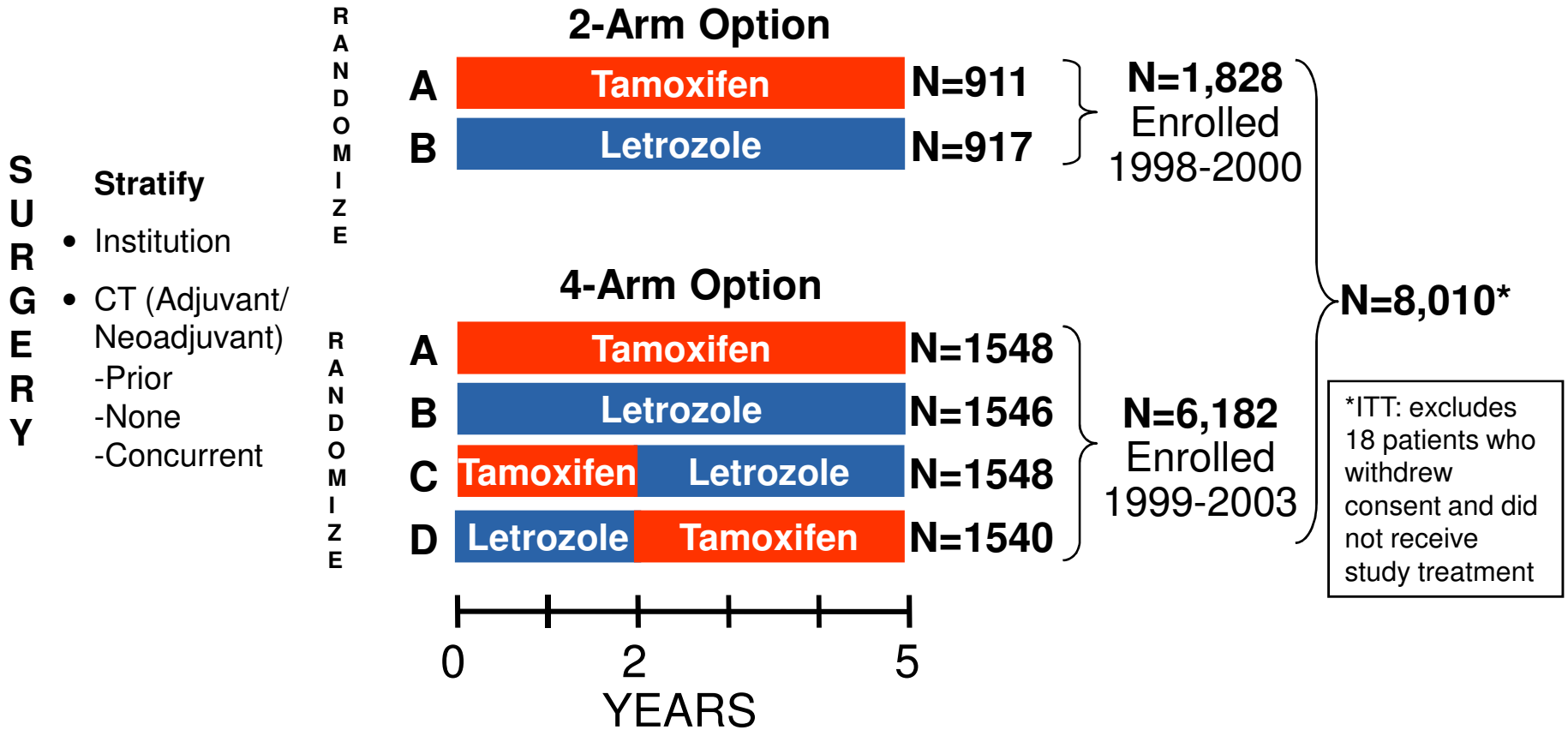
Aromatase Inhibitor Trials



BIG 1-98 Worldwide Collaborative

Argentina	123	New Zealand	157
Australia	667	Peru	51
Belgium	634	Poland	277
Brazil	17	Portugal	64
Canada	20	Russia	240
Chile	22	Slovenia	15
Czech Rep.	109	South Africa	187
Denmark	1396	Spain	70
France	1016	Sweden	64
Germany	113	Switzerland	611
Hungary	334	Turkey	54
Iceland	6	United Kingdom	401
Italy	1285	Uruguay	1
Netherlands	94	**TOTAL**	**8028**

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

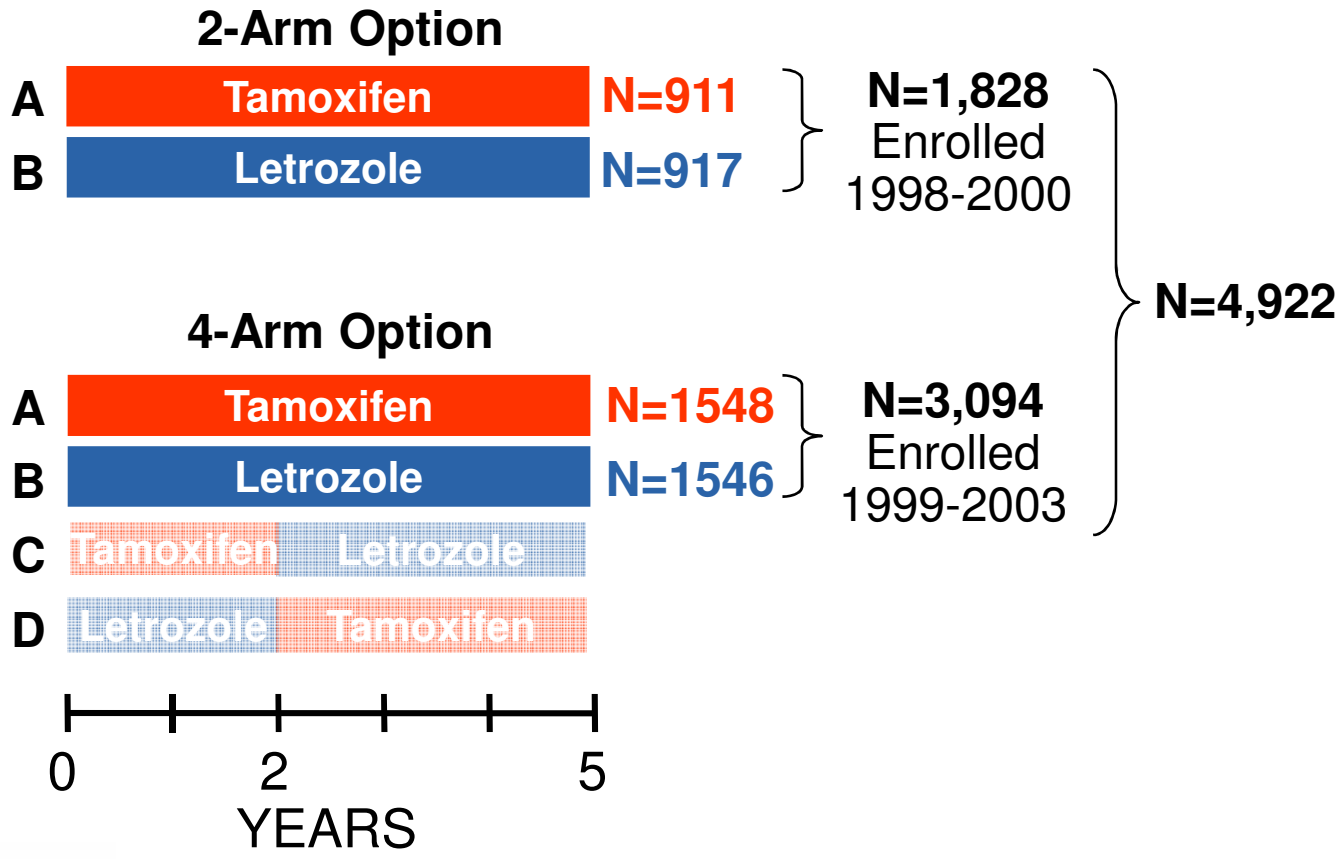
Coates et al, J Clin Oncol 2007;25:486-92

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



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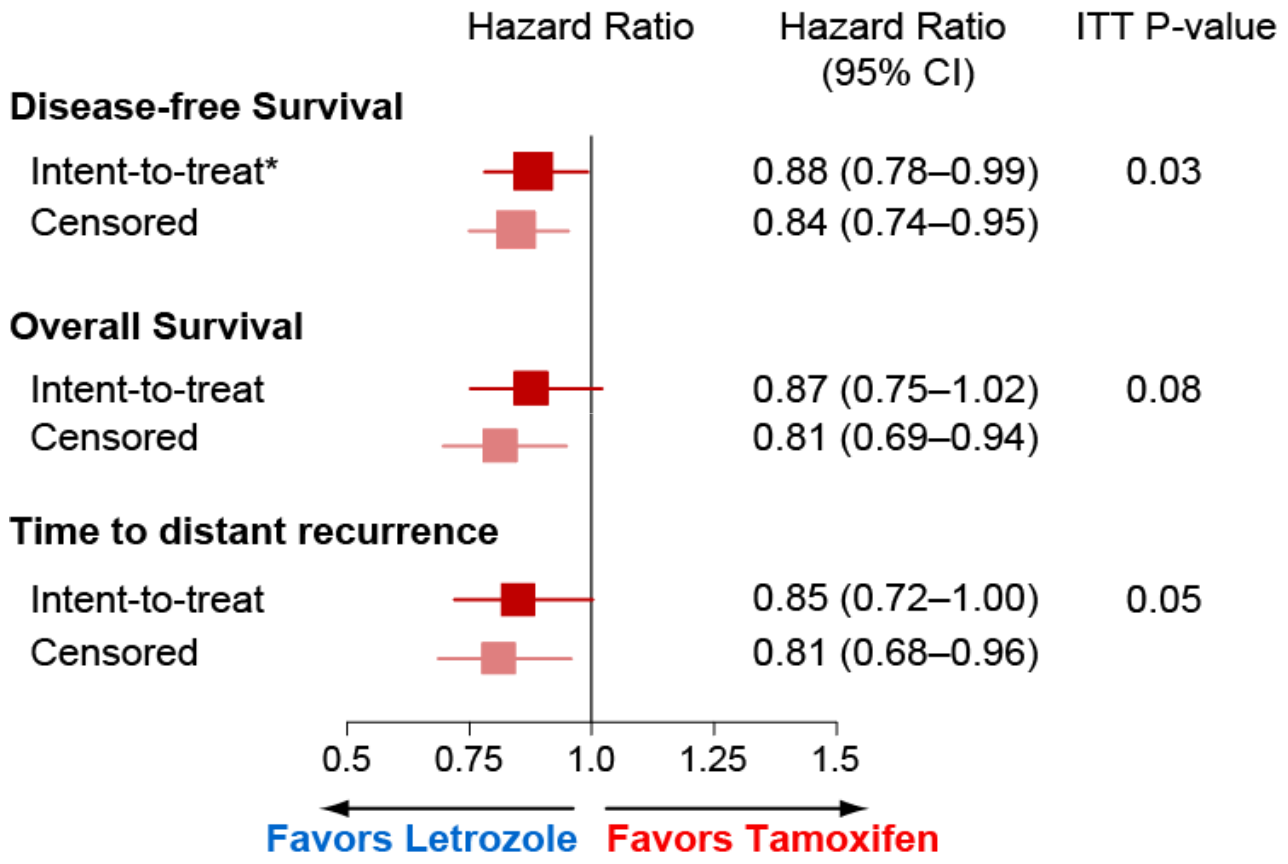
BIG 1-98 Monotherapy Update

- 2005 results of Let superiority led to unblinding of Tam-alone arm
- 619 (25.2%) patients crossed over from Tam to Let after unblinding mostly in years 3-5
- 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



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

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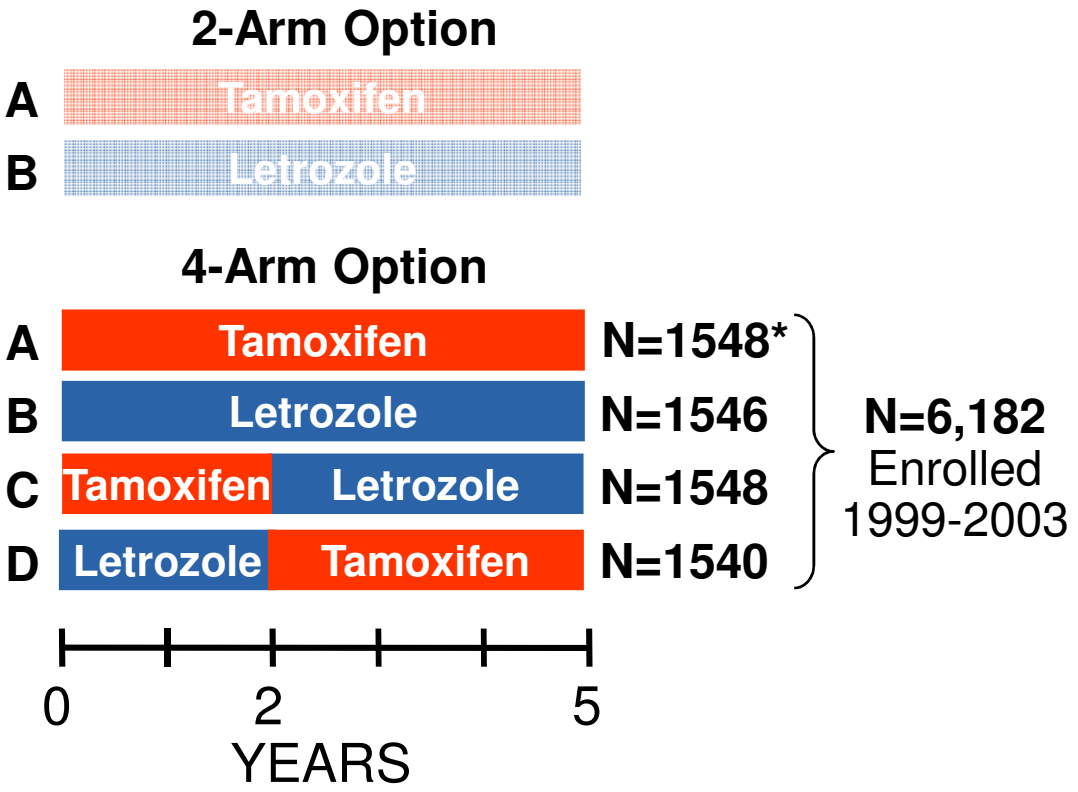
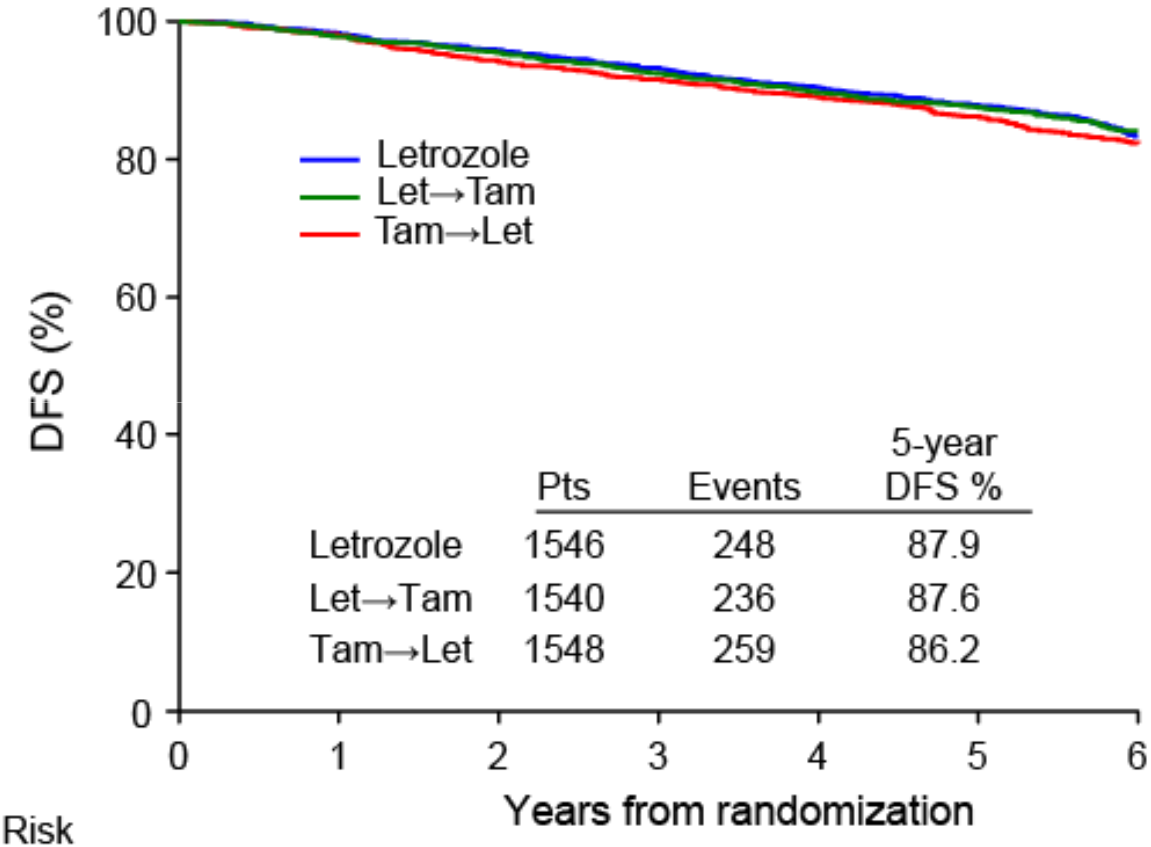
BIG 1-98 Sequential Therapy



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

Is a sequence of agents superior to letrozole monotherapy?

BIG 1-98 Sequential Treatment
Disease-Free Survival

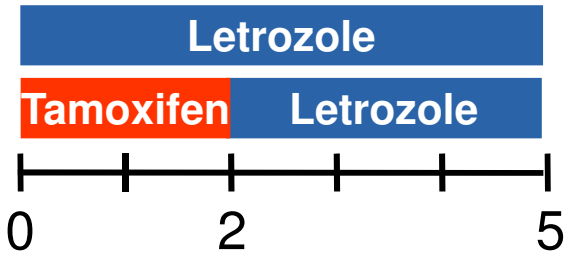


	Pts	Events	5-year DFS %
Letrozole	1546	248	87.9
Let→Tam	1540	236	87.6
Tam→Let	1548	259	86.2

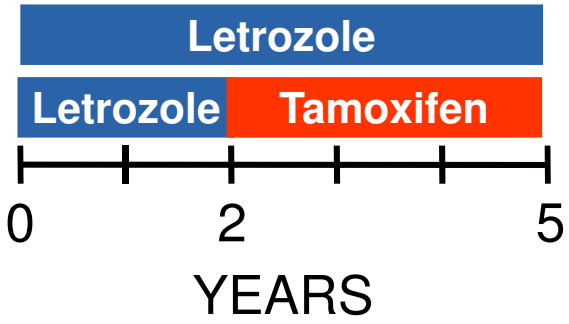
Number at Risk				
Letrozole	1546	1470	1371	565
Let→Tam	1540	1467	1369	546
Tam→Let	1548	1457	1369	561

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



N=3,094

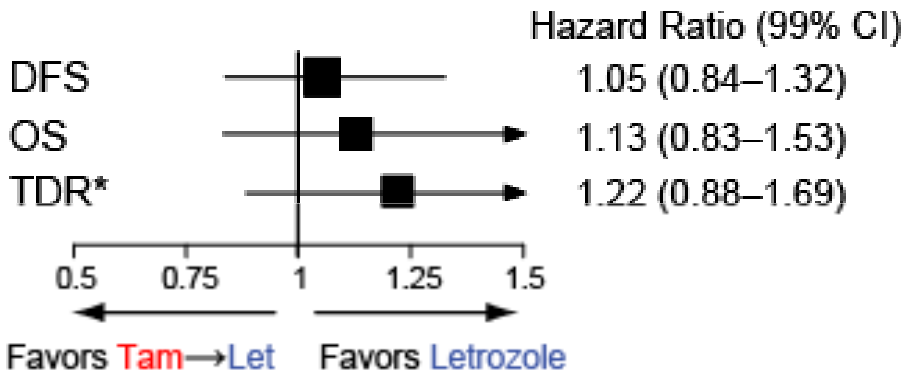


N=3,086

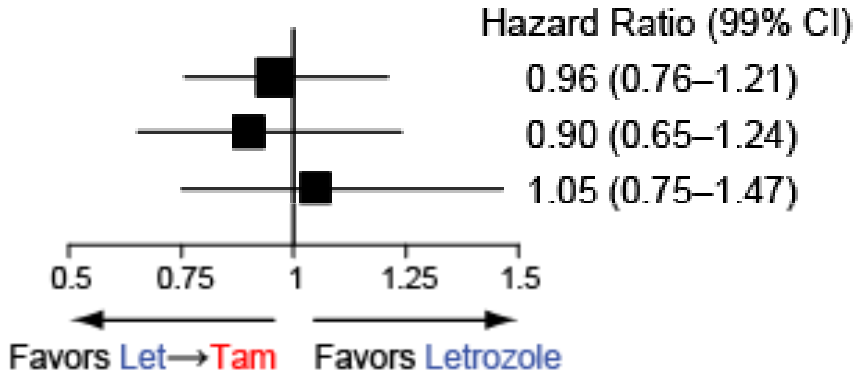
Sequential Treatment Comparisons

Median Follow-up 71 months

Tam→Let vs. Let



Let→Tam vs. Let

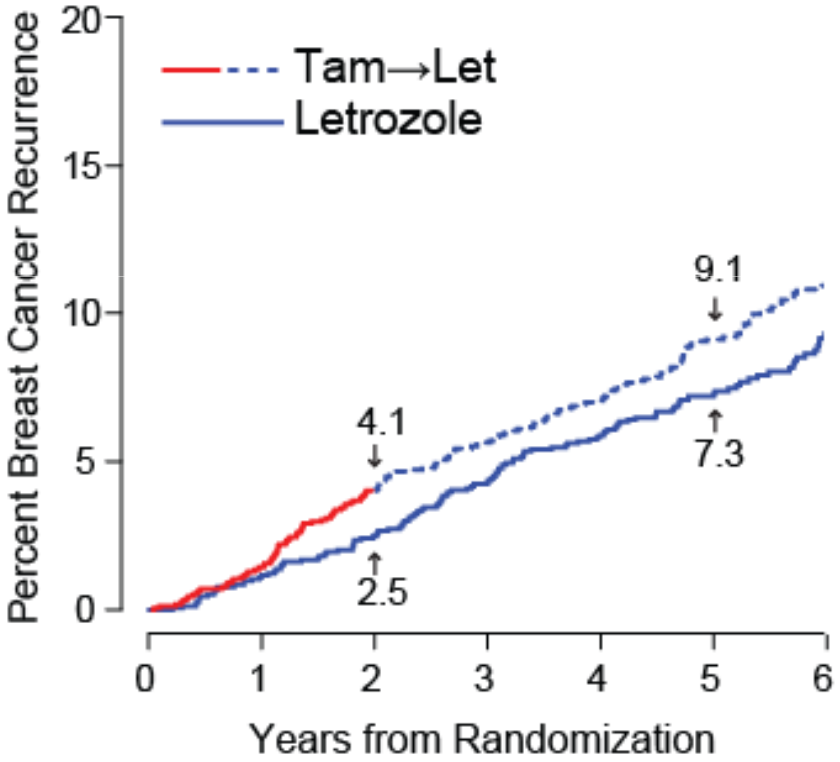


*Time to distant recurrence

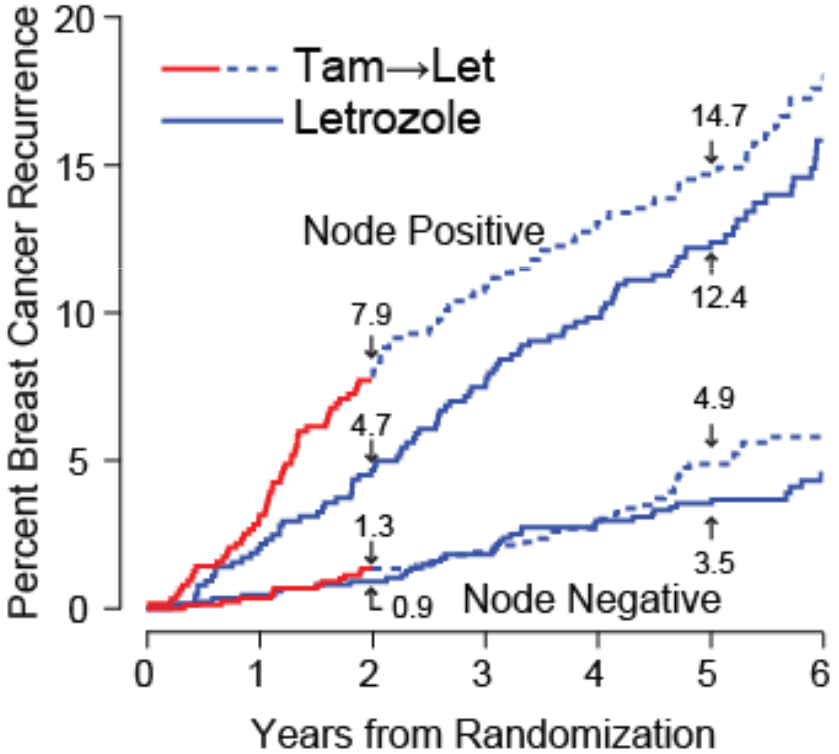
Breast Cancer Events

Tam→Let vs. Let

Overall



By Nodal Status*



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

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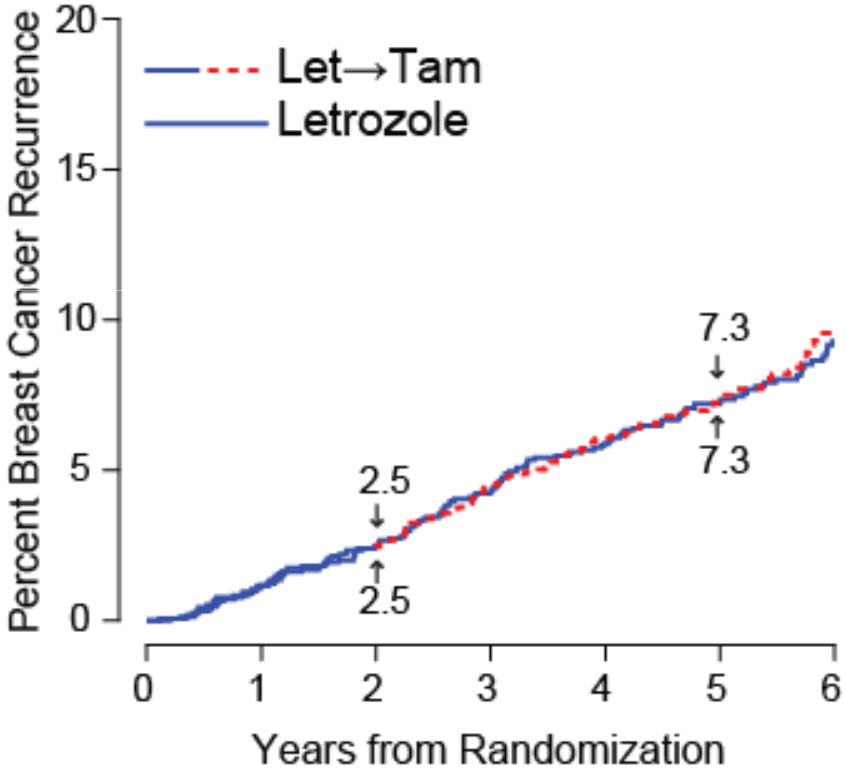
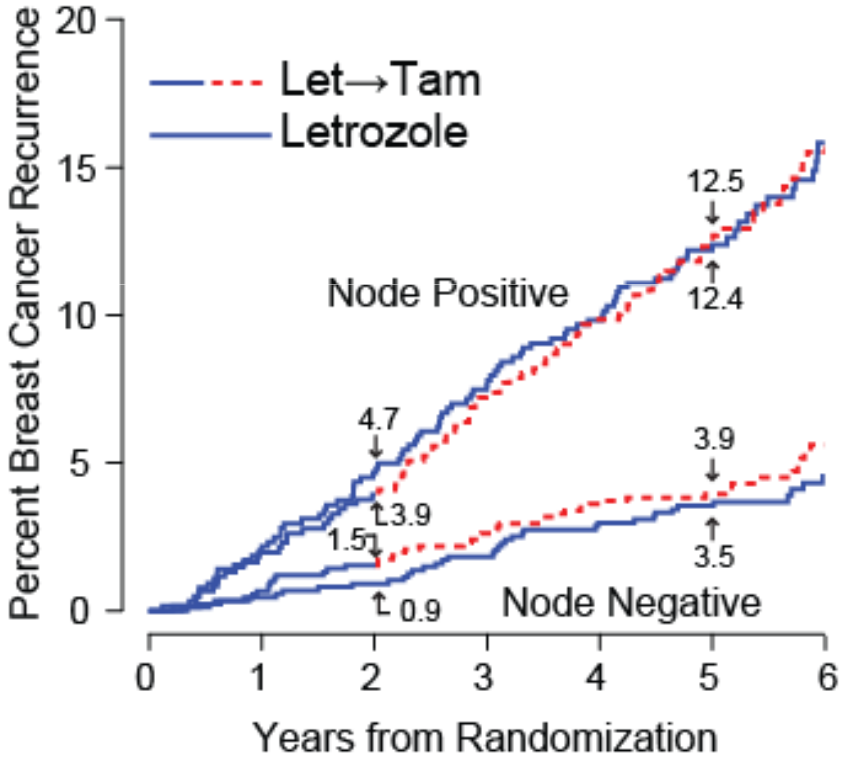
Breast Cancer Events

Let→Tam vs. Let

Overall



By Nodal Status*



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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
- Early reduction of distant events predicted the later effect on overall survival
- 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

BIG 1-98 : Further investigations

- Cross-over after unblinding of arm A
- Cognitive function
- BMD for Swiss patients
- Efficacy and adverse events
- Translational research
  - Molecular profiling from FFPE tissue
  - CYP 2D6 und 19A1
  - GGI and other predictors of responsiveness and resistence

AIs, BIG 1-98 and the clinician

- Best strategy to start with AI
- After 2 years, Let can be switched to tam if required
- Tam remains a valuable option for patients at low risk or with AI intolerance/contraindication
- AIs are safe drugs
- Bone health should be monitored and managed according to well established guidelines
- Databank and translational studies are needed to better tailor endocrine treatments

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

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