

Adjusting for Selective Crossover in Analyses of Letrozole Versus Tamoxifen in the BIG 1-98 Trial

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International Breast Cancer Study Group



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Disclosures

- BIG 1-98 is coordinated by the International Breast Cancer Study Group (IBCSG) for the BIG.
- Novartis, the manufacturer of letrozole, distributed study drugs and provided financial support to IBCSG but imposed no restrictions on the investigators with respect to trial data.
- Statistical analysis partially supported by NCI grant CA-75362 to IBCSG Statistical and Data Management Center.



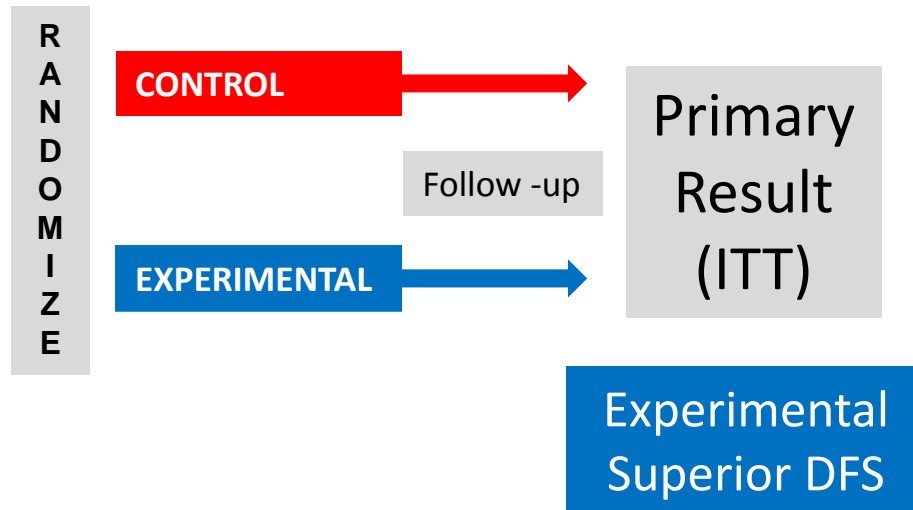
What is Selective Crossover?

- Special case of *non-adherence to a randomized treatment* following the report of *positive trial results*: control group patients selectively cross over to the experimental treatment
- *Disturbs the randomized comparison* in updated analyses performed subsequent to the first results
- BIG 1-98, adjuvant trastuzumab trials



Randomized Clinical Trial

Randomized Trial



Positive primary result leads to ethical imperative to allow patients in control group to receive experimental treatment

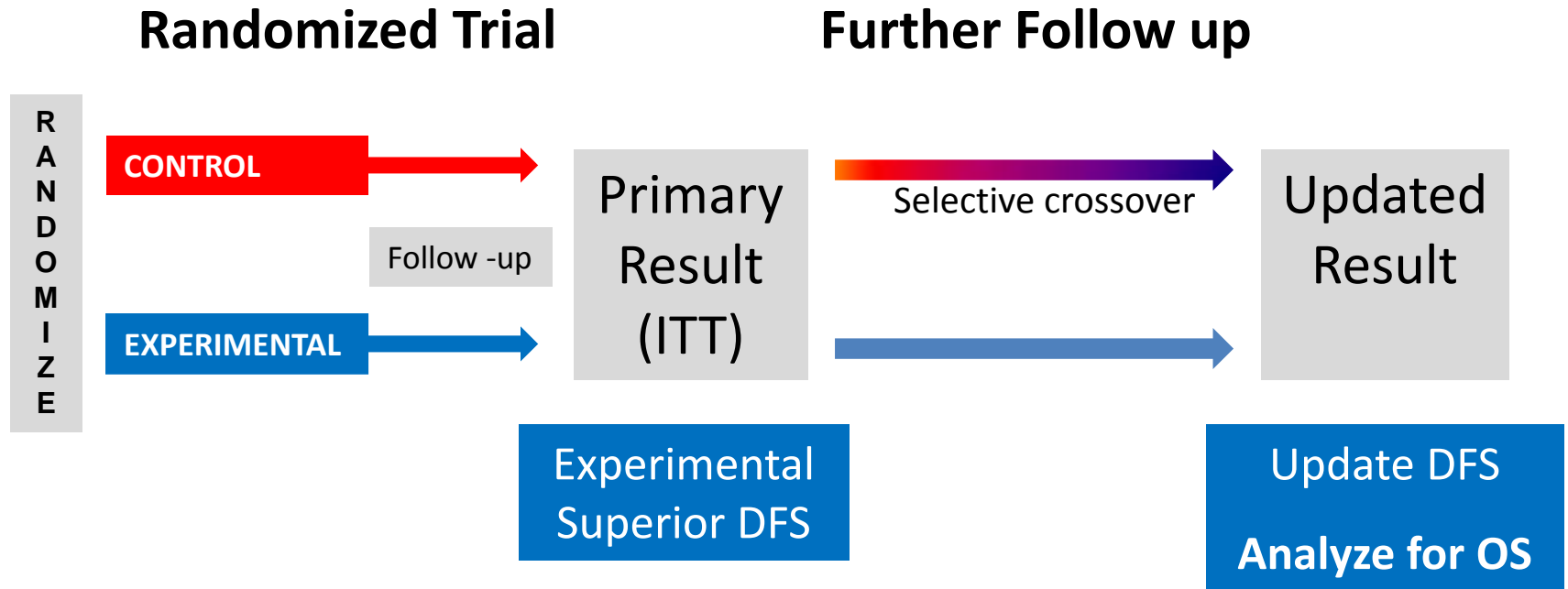


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Randomized Clinical Trial



Paradigm Shift

Randomized
clinical trial



Observational
study

Intent-to-
Treat

Modelling –
account for
treatment selection

Goal: Determine the best estimate of benefit of experimental treatment *had there been no selective crossover*

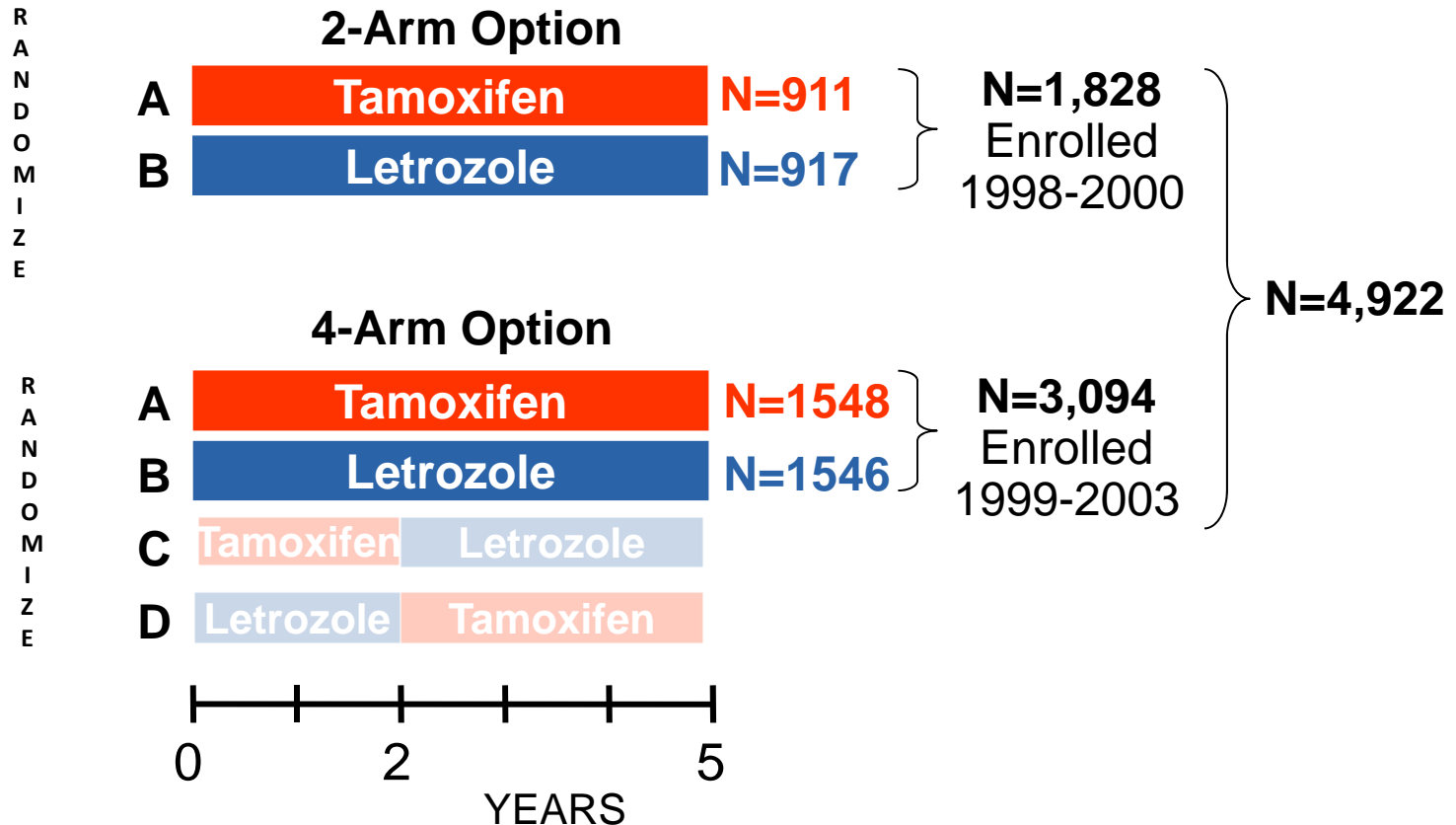


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BIG 1-98 Monotherapy Update

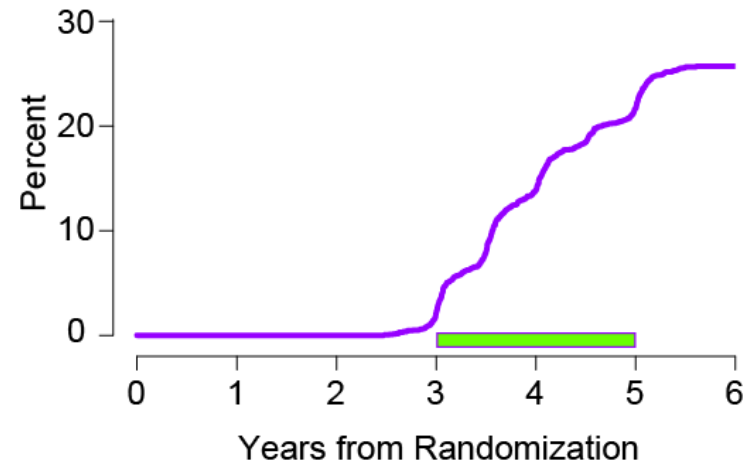
76 months median follow-up (NEJM 2009)



Includes only patients randomized to monotherapy
(directly updates Coates et al., J Clin Oncol 2007 at 51 mos. MFU)

Selective Crossover in Tamoxifen Arm of BIG 1-98

- First report Jan 2005: Let vs. Tam HR for DFS=0.81 (95% CI 0.70-0.93)
- 25% crossed over
- 7% of total follow up
- Average 18 months on Let
- Patient and disease characteristics that contribute to outcome also influence selective crossover



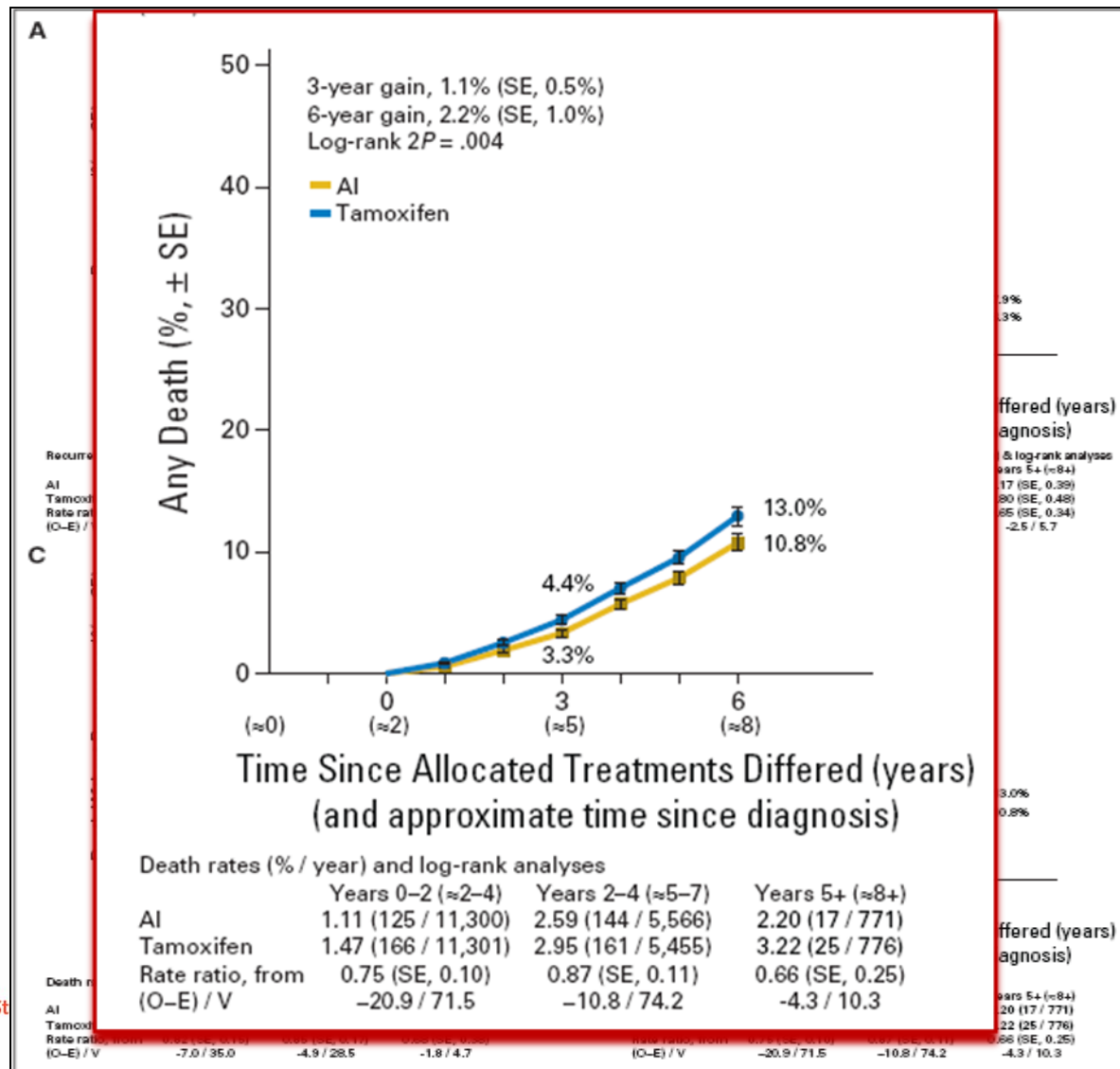
Meta-Analysis of Breast Cancer Outcomes in Adjuvant Trials of Aromatase Inhibitors Versus Tamoxifen

Mitch Dowsett, Jack Cuzick, Jim Ingle, Alan Coates, John Forbes, Judith Bliss, Marc Buyse, Michael Baum, Aman Buzdar, Marco Colleoni, Charles Coombes, Claire Snowdon, Michael Grant, Raimund Jakesz, Manfred Kaufmann, Francesco Boccardo, Jon Godwin, Christina Davies, and Richard Peto

Ingle JN, et al. AIs vs. tamoxifen as adjuvant therapy for postmenopausal women with ER-positive breast cancer: meta-analyses of randomized trials of monotherapy and switching strategies. SABCS 2008, abstract #12.

Cohort 2:
Trials of
switch from
tamoxifen
to AI

Switching to AI
after 2-3 yrs of
tamoxifen
prolongs OS



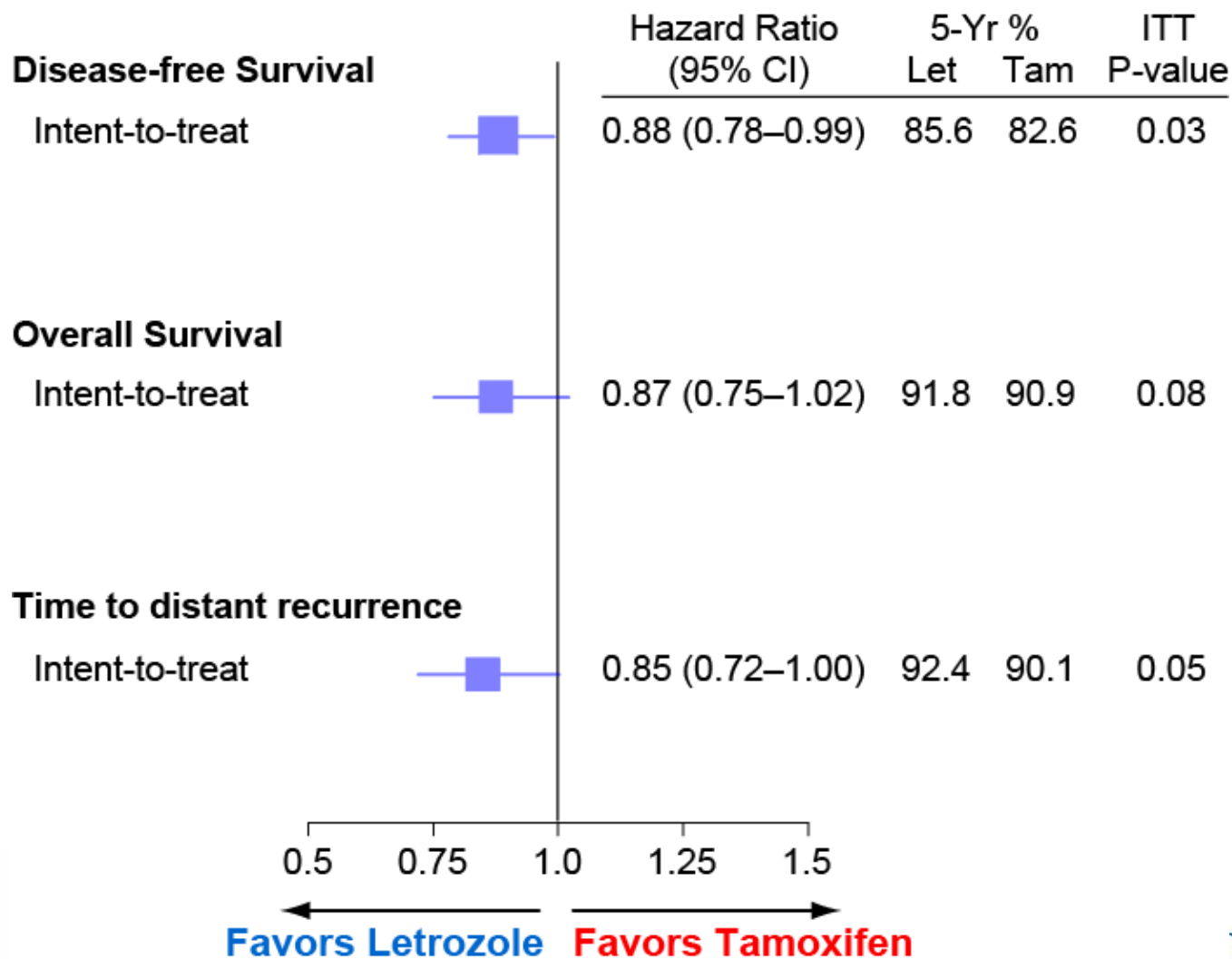
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BIG 1-98 Monotherapy Update

76 months median follow-up (NEJM 2009)



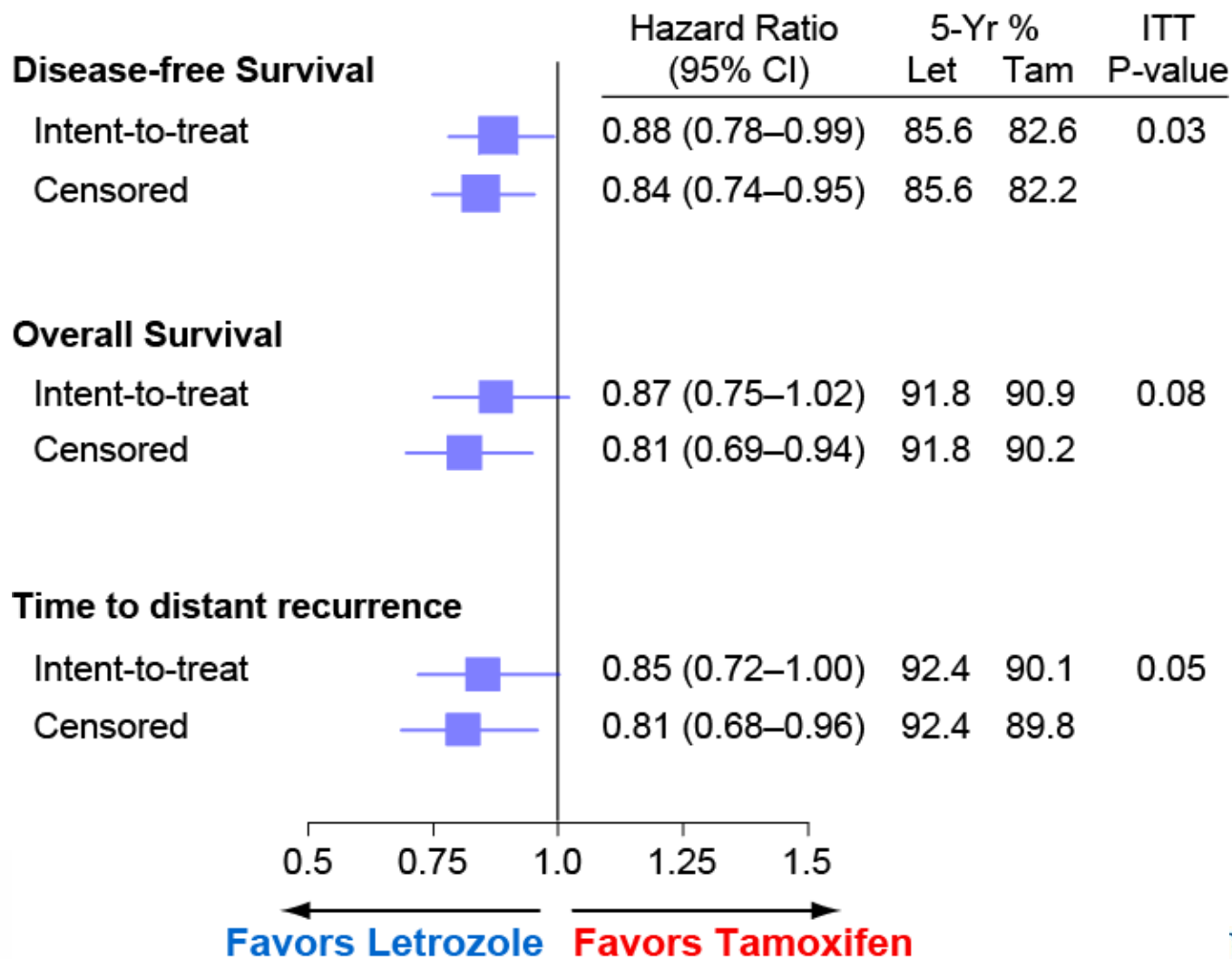
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76 months median follow-up (NEJM 2009)



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Inverse Probability of Censoring Weighted Analysis (IPCW)

- Weight the follow up for the women who stay on **tamoxifen** so that they account *not only* for themselves *but also* for the censored follow up of matched patients who cross over
- Weights determined by **matching characteristics**, both baseline and across time, for the women who do and do not cross over
- Better estimate of treatment effect than ITT in the presence of selective crossover
- Assumes all important confounders of both crossover and outcome are used to estimate weights

Robins JM, Finkelstein DM. Biometrics 2000; 56:779-88



Overall Survival

Analysis	Mo/Yr Presented	Median Follow Up (mos.)	Number of Events	HR [Let:Tam] (95% CI)
ITT	1/05	26	358	.86 (.70-1.06)
ITT	12/08	76	646	.87 (.75-1.02)
Censored	12/08	74 ⁺	641 ⁺	.81 (.69-.94)
IPCW*	Today	74 ⁺	641 ⁺	.83 (.71-.97)

+ Follow up censored at selective crossover: 641 events and 74 mos. median follow up.

* The weighting adjusts for factors associated with OS and with selective crossover, including baseline factors such as age, nodal status, tumor grade, and time-varying performance status.



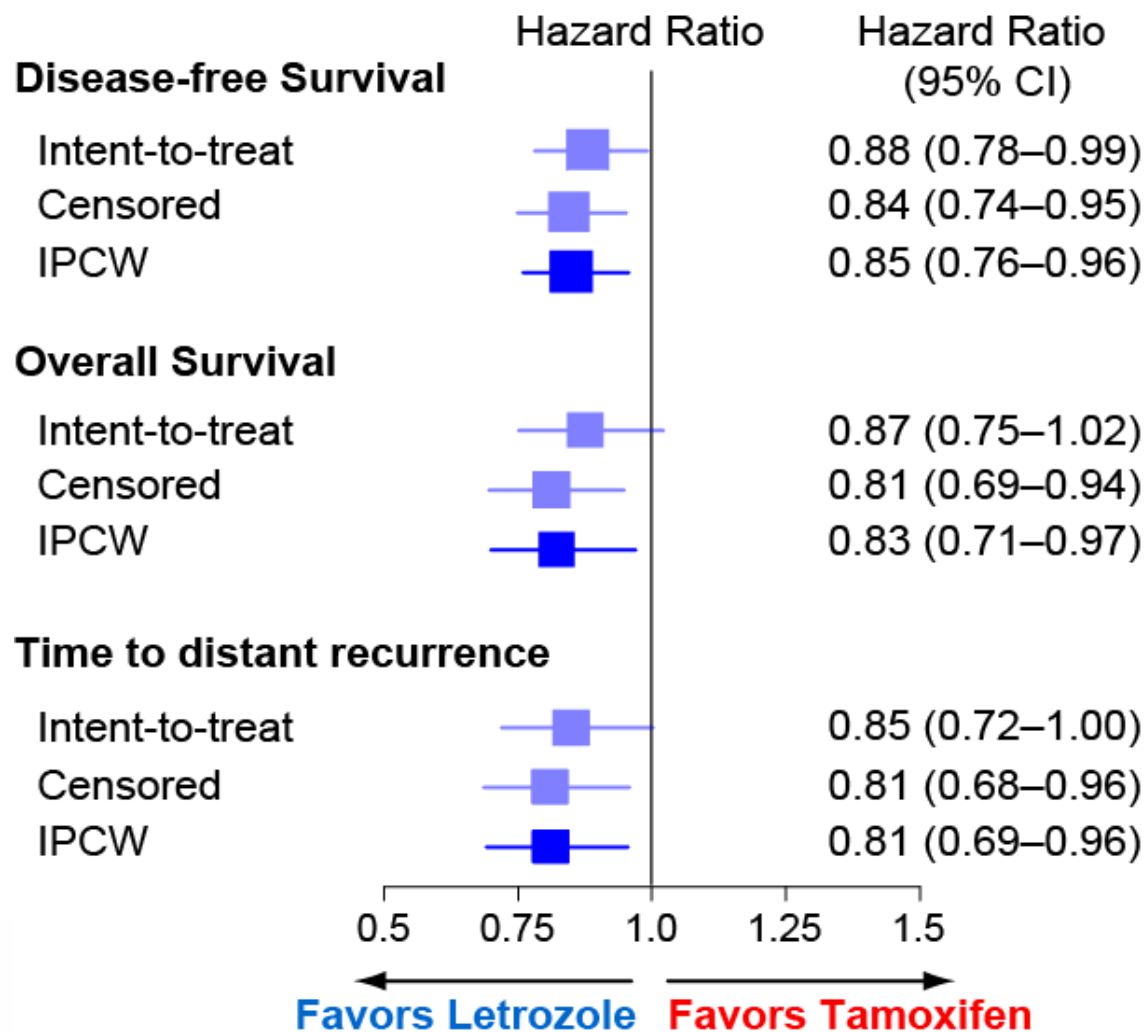
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BIG 1-98 Monotherapy Update

Including IPCW Analyses



Conclusions

- Because of selective crossover and based on external evidence showing the benefit of switching from tamoxifen to an aromatase inhibitor, the ITT analysis on updated data from BIG 1-98 is inaccurate and no longer relevant for patient care
- Modeling methods such as IPCW should be used to estimate outcome that would have been observed *had there been no selective crossover*
- BIG 1-98 provides evidence of a statistically significant ($p < 0.05$) overall survival benefit for 5 years of letrozole compared with 5 years of tamoxifen



Thanks to...

- The patients participating in the trial
- The investigators, data managers, nurses, study coordinators, statisticians
- The cooperative groups
- The trial monitors/audit teams
- Novartis

